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(54) Cyclic peptide antifungal agents and process for preparation thereof

Zyklische Peptide mit antifungischer Wirkung und Verfahren zu ihrer Herstellung

Dérivés cyclopeptidiques antifongiques et procédé de leur préparation

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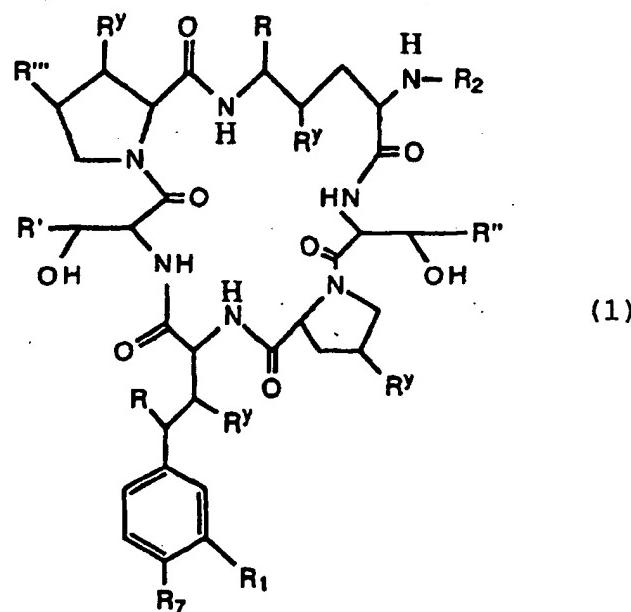
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D scripti n**Ba kground of th Inv ntion**

- 5 [0001] This invention relates to cyclic peptide antifungal agents. In particular, it relates to acyl derivatives of the echinocandin class of cyclic peptide antifungal agents; to methods for treating antifungal and parasitic infections, and to formulations useful in the methods.
- 10 [0002] The compounds provided by this invention are semi-synthetic antifungal agents in that they are derived from the cyclic peptide antifungals which are produced by culturing various microorganisms. A number of cyclic peptide antifungals are known. Among these are echinocandin B (A30912A), aculeacin, mulundocandin, sporiofungin, L-671,329, FR901379, and S31794/F1. All such antifungals are structurally characterized by a cyclic hexapeptide core, or nucleus, the amino group of one of the cyclic amino acids bearing a fatty acid acyl group forming a side chain off the core or nucleus. For example, echinocandin B has a linoleoyl side chain while aculeacin has a palmitoyl side chain. These fatty acid side chains of the cyclic hexapeptides can be removed by enzymatic deacylation to provide the free nucleus. (Formula (1), hereinafter, wherein R₂ is hydrogen.) Reacylation of the amino group of the nucleus provides semisynthetic antifungal compounds. For example, the echinocandin B nucleus provides a number of antifungal agents when reacylated with certain unnatural side chain moieties (see *Debono*, U.S. Pat. No. 4,293,489). Among such antifungal compounds is cilofungin which is represented by the formula (1) wherein R is methyl, R₁ is hydrogen and R₂ is p-(n-octyloxy)benzoyl.
- 15 [0003] Enzymatic deacylation of the cyclic hexapeptides is carried out with deacylase produced by the organism *Actinoplanes utahensis* and related microorganisms as described by *Abbott et al.*, U.S. Pat. No. 4,293,482.
- 20 [0004] The present invention provides acylated cyclic hexapeptides having unique side chain acyl groups which, *inter alia* impart enhanced antifungal and antiparasitic potency e.g. against pathogenic strains of *Candida albicans*. Also provided is a process for removing the aminal and benzylic hydroxy groups to result in a dideoxy compound of formula (1) (R = H).

Summary of the Invention

- 30 [0005] The compounds provided by this invention are represented by the following formula (1):

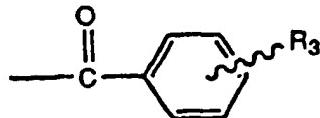


55 wherein

R' is hydrogen, methyl or NH₂C(O)CH₂;
R'' and R''' are independently methyl or hydrogen;

R and R^y are independently hydroxy or hydrogen;
R₁ is hydroxy, hydrogen or hydroxysulfonyloxy;
R₇ is hydroxy, hydrogen, hydroxysulfonyloxy or phosphonooxy; and

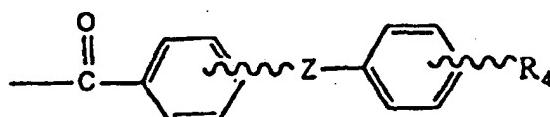
5 I) R₂ is a substituted benzoyl group represented by the formula



wherein

15 R₃ is quinolyl; or

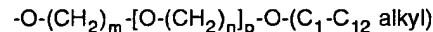
II) R₂ is an acyl group represented by the formula



25 wherein

Z is -C≡C-, -CH=CH-, or a carbon to carbon bond;

- 30 A) R₄ is C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, C₃-C₁₂ cycloalkoxy, naphthyl, pyridyl, thiienyl, benzothienyl, quinolyl or phenyl; or
B) R₄ is phenyl substituted by amino, C₁-C₁₂ alkylthio, halogen, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₁-C₁₂ substituted alkyl, C₂-C₁₂ substituted alkenyl, C₂-C₁₂ substituted alkynyl, C₁-C₁₂ alkoxy, trifluoromethyl, phenyl, substituted phenyl, phenyl substituted with a polyoxa-alkyl group represented by the formula



40 wherein m and n are integers of from 2 to 4, and p is 0 or 1; or

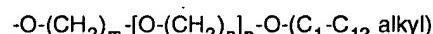
- C) R₄ is phenyl substituted with C₁-C₆ alkoxy substituted by fluoro, bromo, chloro or iodo; or
D) R₄ is a group represented by the formula



wherein

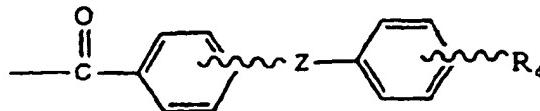
50 Y is -C≡C- or -C=C-; and

- R₆ is C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyl; C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, phenyl, C₃-C₁₂ cycloalkenyl, naphthyl, benzothiazolyl, thiienyl, phenyl substituted by amino, C₁-C₁₂ alkylthio, halogen, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₁-C₁₂ alkoxy, trifluoromethyl, -O-(CH₂)_{p'}-W-R₅ wherein p' is an integer of from 2 to 4; W is pyrrolidino, piperidino or piperazino, and R₅ is hydrogen, C₁-C₁₂ alkyl, C₃-C₁₂ cycloalkyl, benzyl or C₃-C₁₂ cycloalkylmethyl; or C₁-C₆ alkoxy substituted by fluoro, bromo, iodo or chloro; or R₆ is a phenyl substituted by a polyoxa-alkyl group represented by the formula



wherein m, n and p are as defined above; or
 R₂ is an acyl group represented by the formula

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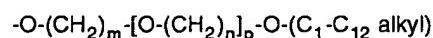
wherein

Z is -C≡C- or -CH=CH-;

15

- A) R₄ is hydrogen, C₂-C₁₂ alkynyl, C₂-C₁₂ substituted alkynyl, C₁-C₁₂ alkoxy; or
- B) R₄ is C₁-C₁₂ alkoxy substituted with C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, C₂-C₁₂ alkynyl, amino, C₁-C₄ alkylamino, di-(C₁-C₄ alkyl)amino, C₁-C₁₂ alkanoylamino, phenyl substituted with a poly-oxa-alkyl group represented by the formula

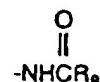
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wherein m, n and p are as defined; or

- C) R₄ is C₁-C₁₂ alkoxy substituted with a group of the formula

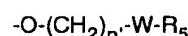
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- wherein R₈ is C₁-C₆ alkoxy optionally substituted with phenyl; or
- D) R₄ is a group represented by the formula

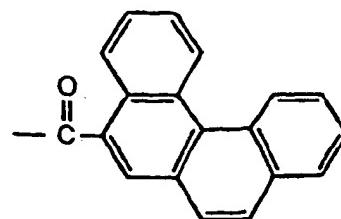
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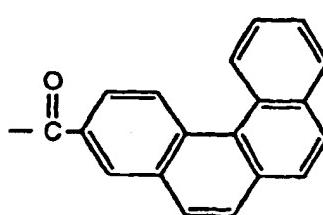
wherein p', W and R₅ are as defined; or

- IV) R₂ is a group having the formula

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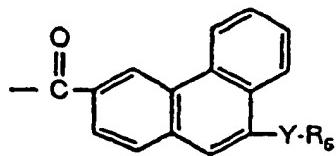
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wherein Y and R₆ are as defined above; or
 10 V) R₂ is naphthoyl substituted with R₄

wherein

- 15 A) R₄ is C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, C₃-C₁₂ cycloalkoxy, naphthyl, pyridyl, thieryl, benzothienyl, quinolyl or phenyl; or
 B) R₄ is phenyl substituted by amino, C₁-C₁₂ alkylthio, halogen, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₁-C₁₂ substituted alkyl, C₂-C₁₂ substituted alkenyl, C₂-C₁₂ substituted alkynyl, C₁-C₁₂ alkoxy, trifluoromethyl, phenyl, substituted phenyl, phenyl substituted with a polyoxa-alkyl group represented by the formula

20 -O-(CH₂)_m-[O-(CH₂)_n]_p-O-(C₁-C₁₂ alkyl)

wherein m, n and p are as defined; or
 25 C) R₄ is phenyl substituted with C₁-C₆ alkoxy substituted by fluoro, bromo, chloro or iodo; or
 D) R₄ is a group represented by the formula

-Y-R₆

30 wherein

Y has the same meanings as defined above; and
 R₆ is C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyl; C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, phenyl, C₃-C₁₂ cycloalkenyl, naphthyl, benzothiazolyl, thieryl, phenyl substituted by amino, C₁-C₁₂ alkylthio, halogen, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₁-C₁₂ alkoxy, trifluoromethyl, -O-(CH₂)_p-W-R₅, or C₁-C₆ alkoxy substituted by fluoro, bromo, iodo or chloro; or
 R₆ is a phenyl substituted by a polyoxa-alkyl group represented by the formula

40 -O-(CH₂)_m-[O-(CH₂)_n]_p-O-(C₁-C₁₂ alkyl)

wherein m, n and p are as defined above; and the pharmaceutically acceptable non-toxic salts thereof.

[0006] Also provided are formulations and methods for inhibiting parasitic and fungal activity which employ the compounds of the invention, and a process for preparing the dideoxy form of the compounds.

Detailed Description

[0007] The term: "C₁-C₁₂ alkyl" refers to the straight or branched chain alkyl hydrocarbon groups such as, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl groups; and the like.

[0008] The term "C₂-C₁₂ alkenyl" refers to groups such as vinyl, 1-propene-2-yl, 1-butene-4-yl, 1-pentene-5-yl, 1-butene-1-yl, and the like.

[0009] The term "C₂-C₁₂ alkynyl" refers to such groups as ethynyl, propynyl, pentynyl, butynyl and the like.

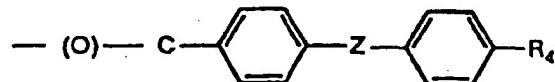
[0010] The term "C₁-C₁₂ alkylthio" refers to such groups as methylthio, ethylthio, t-butylthio, and the like.

[0011] The term "C₁-C₁₂ alkoxy" refers to the straight or branched chain oxyalkyl groups such as, e.g. methoxy, ethoxy, propoxy, butoxy, heptoxy, octyloxy, dodecyloxy, and the like.

[0012] The term C₃-C₁₂ cycloalkoxy" refers to such groups as cyclopropoxy, cyclobutoxy and the like.

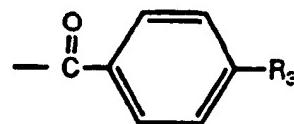
- [0013] The term "C₃-C₁₂ cycloalkenyl" refers to such groups as cyclopropenyl, cyclobut enyl, cyclopentenyl, and the like.
- [0014] The term "C₁-C₁₂ substituted alkyl," "C₂-C₁₂ substituted alkenyl", and "C₂-C₁₂ substituted alkynyl", denotes the above substituted one or two times with halogen, hydroxy, protected hydroxy, amino, protected amino, C₁-C₇ acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carbamoyloxy, cyano, methylsulfonylamino, phenyl, substituted phenyl, or C₁-C₁₂ alkoxy.
- [0015] The term "substituted phenyl" is represented by a phenyl group substituted with one, two, or three moieties chosen from halogen, hydroxy, protected hydroxy, cyano, nitro, C₁-C₁₂ alkyl, C₁-C₁₂ alkoxy, carboxy, protected carboxy, carboxymethyl, hydroxymethyl, amino, aminomethyl trifluoromethyl or N-(methylsulfonylamino)
- [0016] The term "C₃-C₁₂ cycloalkyl" refers to such groups as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.
- [0017] The term "C₁-C₄ alkylamino" refers to such groups as methylamino, ethylamino, n-butylamino and the like.
- [0018] The term "di-(C₁-C₄ alkyl)amino" refers to such groups as dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino, methylethylamino, methyl-n-butylamino, and like tertiary amino groups.
- [0019] The term "C₁-C₁₂ alkanoylamino" refers to such groups as acylamino groups derived from the C₁-C₁₂ carboxylic acids and are exemplified by formamido, acetalamino, propionylamino, butyrylamino, and the like,
- [0020] The term "C₃-C₇ cycloalkylmethyl" refers to those C₃-C₇ cycloalkyls described above further substituted by methyl.
- [0021] The terms "C₇-C₁₀ bicycloalkyl" and "C₇-C₁₄ tricycloalkyl" refer to such groups as bicyclo[2.2.1.]hept-2-yl, bicyclo[2.2.1.]hep-4-en-2-yl, bicyclo[3.3.1.]nona-3-yl, bicyclo[3.3.1.]nona-2-yl, bicyclo[3.2.1.]oct-2-yl, bicyclo[2.2.2.]oct-2-yl, bicyclo[2.2.2]oct-5-en-2-yl, adamantlyl and the like.
- [0022] The term "dideoxy" refers to compounds of the formula (1) wherein R=H.
- [0023] The term "inhibiting", such as used in relation to the methods for inhibiting parasitic and fungal activity, is defined to mean its normal definition, i.e., to stop, retard or prophylactically hinder or prevent.
- [0024] The term "activity", as used in relation to parasitic and fungal activity, includes growth thereof and attending characteristics and results from the existence of the parasite or fungus.
- [0025] The term "contacting", as used in relation to the methods for inhibiting parasitic and fungal activity by contacting a compound of the invention with a parasite or fungus, is defined to mean its normal definition. However, the term does not imply any further limitations to the process, such as by mechanism of inhibition, and the methods are defined to encompass the spirit of the invention, which is to inhibit parasitic and fungal activity by the action of the compounds and their inherent anti-parasitic and anti-fungal properties, or in other words, the compounds, used in the method are the causative agent for such inhibition.
- [0026] Examples of acyl groups wherein R₂ is a group represented by the formula

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- [0027] Examples of such acyl groups wherein R₄ is represented by the formula -Y-R₆ include 4-[4-(phenylethynyl)phenyl]benzoyl, 4-[4-(phenylethynyl)-phenoxy]benzoyl, 4-[4-(hexynyl)phenyl]benzoyl, 4-[4-(styryl)phenoxy]benzoyl, 4-[4-(4-benzylphenylethynyl)-phenyl]benzoyl, 4-[4-(4-methylpiperidino)ethoxy]phenylethynyl]phenyl]benzoyl and like acyl groups. Such acyl groups wherein R₄ is represented by the formula -O-(CH₂)_p-W-R₅ form salts of the basic amino groups of the piperidine and piperazine heterocyclic groups with both organic and inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid and with organic acids such as the sulfonic acids, benzenesulfonic acid, toluenesulfonic acid, methanesulfonic acid, acetic acid, chloroacetic acid, trifluoroacetic acid, benzoic acid, isophthalic acid, salicylic acid, citric acid, malic acid, succinic acid, malonic acid and like acids.
- [0028] The following tables contain further examples of the cyclic peptides represented by the formula (1). Table 1 contains examples of cyclic peptides wherein the acyl group R₂ is of the formula

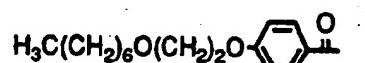
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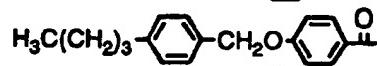
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Table 1R₂

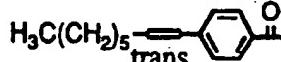
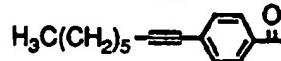
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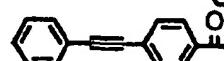
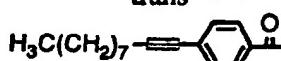
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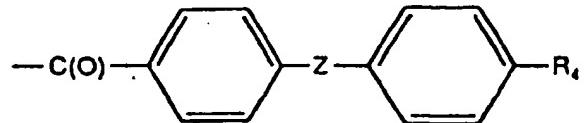


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[0029] The following Table 2 illustrates the compound of the formula (1) wherein R₂ is represented by the formula
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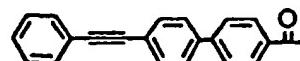
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Table 2R₂

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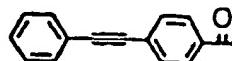
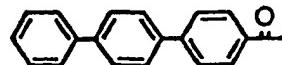


Table 2 continued5
R₂

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[0030] The acyl cyclohexapeptides represented by formula (1) exhibit antiparasitic activity, for example, they are especially active against the infectious fungi Candida albicans and Candida parapsilosis. They also exhibit significant activity against Aspergillus fumigatus. They are active both in vitro and in vivo and accordingly are useful in combating systemic fungal infections.

[0031] The compounds of the invention also inhibit the growth of certain organisms primarily responsible for opportunistic infections in immunosuppressed individuals. For example the compounds of the invention inhibit the growth of Pneumocystis carinii the causative organism of pneumocystis pneumonia in AIDS sufferers.

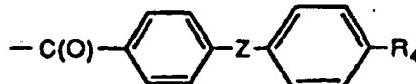
[0032] The antifungal activity of the compounds of the invention is determined in vitro in standard agar dilution tests and disc-diffusion tests wherein minimum inhibitory concentrations of the test compounds obtained. Standard in vivo tests in mice are used to determine the effective dose of the test compounds in controlling systemic fungal infections.

[0033] Tables 4A-E below contain the minimum inhibitory concentrations (MIC) in micrograms per milliliter (mcg/ml) for compounds of the invention against Candida albicans and Candida parapsilosis, and for certain compounds, the effective dose, ED₅₀, in mice.

[0034] In Tables 4A-E, R'=CH₃, R''=CH₃, R^y=OH, R₇=OH and R₁=H, In Tables 4A-D, R=OH, while in Table E, R=H.

[0035] In Table 4C, R₂ is of the formula

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where Z is a carbon-carbon bond and R₄ is as indicated.

TABLE 4C

R ₄	MIC (mcg/ml)		ED ₅₀ (mg/ml)
	C.alb.	C.parap.	
-C≡C-C ₄ H ₉	0.039	2.5	1.20
-C≡C-C ₆ H ₅	0.039	0.625	0.60
-C ₆ H ₅	0.078	10	1.3

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[0036] The non-dideoxy compounds of the invention (formula (1) are prepared with the amino nuclei of the cyclic hexapeptides which are represented by the formula when R₂ is hydrogen. These amino nuclei are obtained from the known natural products by the known enzymatic deacylation by which the fatty acid side chains of the natural compounds are removed. For example, echinocandin B which can be represented by the formula (1) wherein R'=R''=R'''=methyl, R is OH, R^y is hydroxy, R₁ is H, R₇ is OH, and R₂ is linoleoyl, is deacylated to provide the echinocandin B nucleus (R₂=H) with the deacylase produced by the organism Actinoplanes utahensis as described by U.S. Patent Nos. 4,293,482 and 4,304,716.

[0037] The known natural cyclic hexapeptides which are N-deacylated to provide the amino nuclei starting materials include echinocandin B (also known as A-30912A), aculeacin (palmitoyl side chain), tetrahydroechinocandin B (stearoyl side chain), mulundocandin (branched C₁₅ side chain), L-671,329 (C₁₆ branched side chain), S 31794/F1 (tetradecanoyl side chain), sporiofungin (C₁₅ branched side chain) and FR901379 (palmitoyl side chain). The amino nuclei obtained by the N-deacylation are then acylated by employing known amino acylation procedures to provide the N-

acyl cyclic hexapeptides represented by the formula (1) wherein R₂ represents the acyl groups defined hereinabove. The acylating moiety is preferably an active ester of the carboxylic acid RCOOH such as the 2,4,5-trichlorophenyl ester. The R₂COOH precursor acids are prepared by the hydrolysis of the nitrile R₂CN or the ester R₂COOC₁-C₄ alk. These nitrile and ester intermediates are prepared by known methods.

- 5 [0038] The alkoxy aromatic (ie. phenyl and biphenyl) compounds of Tables 9-10 are prepared by one of the two following procedures:

A. The hydroxyaromatic compound (1 equivalent) is dissolved in acetonitrile (200-300 ml) and a base, such as potassium t-butoxide or potassium carbonate (1-equivalent), is added. An alkyl bromide, iodide, or p-toluenesulfonate (1 equivalent) is then added and the solution is refluxed for 6 hours. The solvent is evaporated in vacuo and the residue is dissolved in ether and 2N sodium hydroxide. The ether layer is dried over magnesium sulfate and evaporated to give the alkoxyaromatic product.

10 B. The hydroxyaromatic compound (1 equivalent), alkyl alcohol (1 equivalent), and triphenylphosphine (1 equivalent) are dissolved in tetrahydrofuran (200-300 ml) and diethylazodicarboxylate (1 equivalent) is added dropwise over 10 minutes at room temperature. After 17 hours the solvent is removed in vacuo and the residue is dissolved in ether. This organic layer is extracted with 2N sodium hydroxide solution, dried over magnesium sulfate, and evaporated to give a product which is crystallized from ether/pentane or, if the product contains a tertiary amine, the hydrochloride salt is formed and crystallized from methanol/ethyl acetate.

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Table 9

<u>Alkylhalide or tosylate</u>	<u>Wt.</u> g	<u>Method</u>	<u>R</u>	<u>Wt.</u> g
$\text{I}(\text{CII}_2\text{CII}_1)_3$	2.6	A	$-(\text{CH}_2)_2\text{CH}_3$	4.4
$\text{H}_3\text{C}-\text{C}_6\text{H}_3-\text{SO}_3-(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CH}_3$	2.7	A	$-(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CH}_3$	2.6
$\text{H}_3\text{C}-\text{C}_6\text{H}_3-\text{SO}_3-(\text{CH}_2)_2\text{OC}(\text{CH}_3)_3$	2.7	A	$-(\text{CH}_2)_2\text{OC}(\text{CH}_3)_3$	2.6

Table 10

<u>Alkylhalide or tosylate</u>	<u>Wt.</u> g	<u>Method</u>	<u>R</u>	<u>Wt.</u> g
$\text{I}(\text{CII}_2\text{CII}_1)_3$	3.8	A	$-(\text{CH}_2)_2\text{CH}_3$	1.4
$\text{H}_3\text{C}-\text{C}_6\text{H}_3-\text{SO}_3-(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CH}_3$	3.6	A	$-(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CH}_3$	5.1
$\text{H}_3\text{C}-\text{C}_6\text{H}_3-\text{SO}_3-(\text{CH}_2)_2\text{OC}(\text{CH}_3)_3$	4.9	A	$-(\text{CH}_2)_2\text{OC}(\text{CH}_3)_3$	5.2

[0039] The alkynyl and alkenyl aromatic compounds contained in Tables 11-14 are prepared by the following procedure:

[0040] An aromatic bromide, iodide, or trifluoromethane-sulfonate (1 equivalent) is dissolved in acetonitrile (600 ml/0.1 mole of aromatic reactant) under a nitrogen atmosphere. An alkyne or alkene (1 equivalent), triethylamine (2 equivalents), palladium dichloride (0.05 equivalents), triphenylphosphine (0.1 equivalents), and cuprous iodide (0.025 equivalents) are added and the solution is refluxed for 17 hours. The solvent is removed in vacuo and the residue is slurried in ether (300 ml). Solids are removed by filtration and the filtrate is washed with 1N hydrochloric acid solution. The organic layer is dried over magnesium sulfate and evaporated to yield the product.

TABLE 11

<u>Acetylene or olefin</u>	<u>wt.</u> g	<u>wt.</u> g	<u>R</u>	<u>wt.</u> g
	12.1	28.8		26.2
	6.1	14.4		0.6
	15.2	28.8		28.1
	1.9	5.1		1.9
	4.3	11.5		11.2

TABLE 12

<u>Acetylene</u>	<u>wt.</u> g	<u>wt.</u> g	<u>R</u>	<u>wt.</u> g
	1.8	6.0		2.6
	1.4	6.0		5.1
	10.9	40.0		23.3

TABLE 13

<u>Acetylene</u>	<u>wt.</u> g	<u>wt.</u> g	<u>R</u>	<u>wt.</u> g
	7.6	11.1		11.4

<u>Acetylene</u>	<u>wt.</u> <u>g</u>	<u>Halide</u>	<u>wt.</u> <u>g</u>	<u>Product</u>	<u>wt.</u> <u>g</u>
	10.5		9.7		10.2
	22.2		34.4		19.4
	1.2		1.2		1.5

[0041] The aromatic boronic acids listed in Table 15 were prepared by the following procedure:

[0042] An aromatic halide (1 equivalent) is cooled to -78°C in tetrahydrofuran solvent. Butyl lithium (1.2 equivalents) is added. After 15 min triisopropyl borate (2 equivalents) is added and after 10 min of stirring the cooling bath is removed. When the reaction has warmed to room temperature water is added to quench the reaction followed by 1N HCl. The organic layer is removed under reduced pressure leaving a solid precipitate which is collected by filtration. This solid is washed with hexane leaving the pure boronic acid.

[0043] The terphenyl esters listed in Table 16 were made in the following manner:

[0044] An aromatic boronic acid (1 equivalent), methyl 4-iodobenzoate (1 equivalent), and potassium carbonate (1.5 equivalents) were mixed in a nitrogen-purged toluene solution. Alternatively, the trichloro phenyl ester of iodobenzoate may be used. Added tetrakis(triphenylphosphine)palladium (0.03 equivalents) and refluxed for 7 hrs. The solution was decanted to remove the potassium carbonate and reduced in *vacuo*. The residue was triturated with acetonitrile and the product solid was collected by filtration.

TABLE 15

$R = Br$	$R = B(OH)_2$
Wt. (g)	Wt. (g)
<chem>O=Cc1ccc(cc1)OCCOC</chem>	6.1
<chem>O=Cc1ccc(cc1)OCCOC(=O)c2ccc(cc2)C</chem>	12.0
<chem>O=Cc1ccc(cc1)OCCOC(=O)c2ccc(cc2)C(=O)OC(=O)c3ccc(cc3)C</chem>	4.1
<chem>O=Cc1ccc(cc1)OCCOC(=O)c2ccc(cc2)C(=O)OC(=O)c3ccc(cc3)C(=O)OC(=O)c4ccc(cc4)C</chem>	13.6
<chem>O=Cc1ccc(cc1)OCCOC(=O)c2ccc(cc2)C(=O)OC(=O)c3ccc(cc3)C(=O)OC(=O)c4ccc(cc4)C(=O)OC(=O)c5ccc(cc5)C</chem>	5.0

TABLE 16

R	$(HO)_2B-C_6H_4-C_6H_4-R$	Wt. (g)	$H_3CO-C_6H_4-C_6H_4-I$	Wt. (g)	$H_3CO-C_6H_4-C_6H_4-C_6H_4-R$	Wt. (g)
$-O(CH_2)_3CH_3$	5.0	3.2				4.2
$-O(CH_2)_4CH_3$	6.0	3.7				5.2
$-O(CH_2)_5CH_3$	3.4		2.8			3.5
$-O(CH_2)_2O(CH_2)_3CH_3$	3.7			3.6		3.7
$-O(CH_2)_2OC(CH_3)_3$	1.8				1.5	2.2

[0045] The aromatic nitriles or carboxylate esters described in Tables 9-16 can be converted to carboxylic acids by

one of the two following hydrolysis procedures:

5 A. An aromatic nitrile is dissolved in ethanol and an excess of 50% sodium hydroxide solution and refluxed for 2 hours. Water is added until a solid precipitates. The precipitate is collected by filtration, added to dioxane and 6N hydrochloric acid solution and refluxed for 17 hours. Water is added and the carboxylic acid product crystallizes and is collected by filtration and dried under vacuum.

10 B. A carboxylate methyl ester is dissolved in methanol, excess 2N sodium hydroxide solution is added and the solution is refluxed for 5 hours. The solution is made acidic with excess hydrochloric acid and water is added until a precipitate forms. The carboxylic acid is collected by filtration and dried under vacuum.

15 [0046] The carboxylic acids are converted to 2,4,5-trichlorophenyl esters shown in Tables 18, 20 and 22-25 by the following general procedure:

20 [0047] The aromatic acid (1 equivalent), 2,4,5-trichlorophenol (1 equivalent), and N,N'-dicyclohexylcarbodiimide (1 equivalent) are dissolved in methylene chloride. The mixture is stirred for 17 hours after which it is filtered. The filtrate is evaporated to dryness and the residue is dissolved in ether, filtered, and pentane is added until crystallization begins. The crystalline product is collected by filtration and dried under vacuum.

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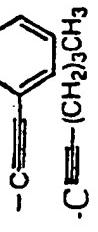
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TABLE 18

	<u>2,4,5-trichlorophenol ester</u>	<u>wt.</u>	<u>g</u>	<u>0.6</u>
	<u>R</u>	<u>wt.</u>	<u>g</u>	
			2.0	
		1.1		0.6

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TABLE 20

<u>R</u>	<u>2,4,5-Trichlorophenol ester</u> <u>wt.</u> <u>g</u>
	1.5

TABLE 22

<u>Carboxylic acid</u> <u>wt.</u> <u>g</u>	<u>2,4,5-Trichlorophenol ester</u> <u>wt.</u> <u>g</u>
	1.2

TABLE 23

<u>R</u>	<u>HO-C(=O)-C₆H₄-C₆H₄-R</u>	<u>2,4,5-Trichlorophenol ester</u>	<u>Wt. (g)</u>
-O(CH ₂) ₃ CH ₃	3.3	4.8	
-O(CH ₂) ₄ CH ₃	3.0	2.5	
-O(CH ₂) ₅ CH ₃	2.3	3.9	
-O(CH ₂) ₂ O(CH ₂) ₃ CH ₃	3.3	4.4	
-O(CH ₂) ₂ OC(CH ₃) ₃	1.3	1.9	

TABLE 24

<u>R</u>	<u>HO-C(=O)-C₆H₄-C≡C-R</u>	<u>2,4,5-Trichlorophenol ester</u>	<u>Wt. (g)</u>
-O(CH ₂) ₃ CH ₃	6.5	5.2	
-O(CH ₂) ₂ O(CH ₂) ₃ CH ₃	4.9	5.2	
-O(CH ₂) ₂ OC(CH ₃) ₃	4.6	2.1	

TABLE 25

<u>R</u>	<u>HO-C(=O)-C₆H₄-C≡C-C₆H₄-R</u>	<u>2,4,5-Trichlorophenol ester</u>	<u>Wt. (g)</u>
-O(CH ₂) ₃ CH ₃	2.9	2.5	
-O(CH ₂) ₂ O(CH ₂) ₃ CH ₃	2.0	1.5	
-O(CH ₂) ₂ OC(CH ₃) ₃	2.0	1.3	

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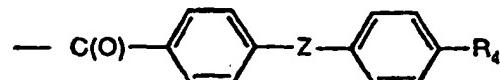
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[0048] The dideoxy compounds of formula (1) are prepared by removing the benzylic and aminal hydroxy groups. The process includes subjecting a non-dideoxy compound of formula (1) (wherein R₂ may be hydrogen or acyl) to a strong acid such as trichloroacetic acid, trifluoroacetic acid or borontrifluoride etherate with trifluoroacetic acid being preferred, and a reducing agent, such as sodium cyanoborohydride or triethylsilane, with triethylsilane being preferred. The reaction takes place at temperatures of between -5 and 70°C, and in a suitable solvent such as methylene chloride, chloroform or acetic acid, with dichloromethane being preferred. The acid should be present in an amount of 2 to 60 moles per mole of substrate, and the reducing agent should be present in an amount of 2 to 60 moles per mole of substrate. This process affords selective removal of the aminal and benzylic hydroxy groups.

[0049] The compounds represented by the formula (1) have improved properties over the previously known N-acyl

hexapeptide antifungals. For example, in general the compounds exhibit oral bioavailability, a property which is important for any systemic antifungal agent. Also, numerous N-acyl compounds of the formula (1) have enhanced antifungal activity and enhanced water solubility.

5 [0050] Among the N-acyl hexapeptides represented by the formula (1) certain are preferred embodiments of the invention. The compounds wherein R₂ is a diphenyl acyl group



wherein Z is a carbon to carbon bond and R₄ is -Y-R₆ and R₆ is C₁-C₁₂ alkyl phenyl or substituted phenyl and Y is an acetylenic bond.

15 [0051] Examples of preferred compounds of the above mentioned group include compounds wherein R₄ is 4-[4-(phenylethynyl)-phenyl]benzoyl and 4-[4-(n-butylethynyl)phenyl]benzoyl.

[0052] Preferred cyclohexylpeptide compounds are represented by the formula 1 wherein R'=R''= methyl, R₁ is hydrogen and R₂ is a preferred acyl group as defined hereinabove.

[0053] Table 26 is a list of the most preferred R₂ substituents, wherein R=R₇=R^y=OH; R'=R''= R'''=CH₃; and R₁=H.

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TABLE 11

<u>Acetylene or olefin</u>	<u>wt.</u> g	<u>R</u>	<u>wt.</u> g
$\text{H}\equiv-(\text{CH}_2)_5\text{CH}_3$	12.1		28.8
$\text{H}\equiv-(\text{CH}_2)_5\text{CH}_3$	6.1		14.4
$\text{H}\equiv-(\text{CH}_2)_7\text{CH}_3$	15.2		28.8
$\text{H}\equiv-\text{C}_6\text{H}_5$	1.9		5.1
$\text{H}\equiv-\text{Si}(\text{CH}_3)_3$	4.3		11.5
			11.2

TABLE 12

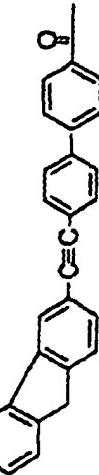
<u>Acetylene</u>	<u>wt.</u> g	<u>R</u>	<u>wt.</u> g
$\text{H}\equiv-\text{C}_6\text{H}_5$	1.8		6.0
$\text{H}\equiv-(\text{CH}_2)_3\text{CH}_3$	1.4		6.0
$\text{H}\equiv-\text{Si}(\text{CH}_3)_3$	10.9		40.0

TABLE 13

<u>Acetylene</u>	<u>wt.</u> g	<u>R</u>	<u>wt.</u> g
$\text{H}\equiv-(\text{CH}_2)_7\text{CH}_3$	7.6		11.1

TABLE 26

R_2	Ester	A30912A Reactant (g)	Nucleus (g)	Product (g)	FABMS
$H_3C(CH_2)_2O$		5.2	6.9	1.4	1142.4951**
$(H_3C)_3CO(CH_2)_2O$		2.1	2.5	2.0	1200.5336**
$H_3C(CH_2)_3O(CH_2)_2O$		5.2	6.4	1.1	1194.5282*
$H_3C(CH_2)_2O$		2.4	3.3	0.9	1136.4832*
$H_3C(CH_2)_3O(CH_2)_2O$		2.0	3.2	3.0	1194.5213*
$(H_3C)_3CO(CH_2)_2O$		1.3	1.5	2.4	1194.5247*
$H_3C(CH_2)_3O(CH_2)_2O$		4.6	7.4	1.3	1126.5025*
$H_3C(CH_2)_3O$		2.5	3.7	5.1	1140.5103*
$H_3C(CH_2)_4O$		3.5	5.0	1.4	1154.5343*
$H_3C(CH_2)_5O$		4.4	6.7	6.5	1170.5234*
$H_3C(CH_2)_3O(CH_2)_2O$		1.9	2.9	1.4	1170.5261*
		1.8	2.6	0.2	1166.4758*



* m+1; ** m+|Li|+

[0054] The N-acylhexapeptides provided by this invention are useful in the treatment of fungal infections both systemic infections and skin infections. Accordingly this invention also provides a method for treating fungal infections in man and animals which comprises administering to said host an antifungally effective non-toxic amount of an N-acylhexapeptide represented by the formula 1. A preferred antifungal method comprises administering an N-acylhex-

apeptide compound where, in formula 1, R'=R"= methyl, R₁ is hydrogen and R₂ is a preferred acyl group as defined hereinabove.

[0055] The antifungal compound can be administered parenterally, e.g. i.m., i.p. or s.c., nasally, orally or can be applied topically for skin infections. The dose administered of course will vary depending on such factors as the nature and severity of the infection, the age and general health of the host and the tolerance of a particular host to the particular antifungal agent. The particular dose regimen likewise may vary according to such factors and may be given in a single daily dose or in multiple doses during the day. The regimen may last from about 2-3 days up to about 2-3 weeks or longer.

[0056] This invention also provides pharmaceutical formulations useful for administering the antifungal compounds of the invention. These formulations comprise an N-acylhexapeptide represented by the formula 1 or a pharmaceutically acceptable, non-toxic salt thereof and a pharmaceutically acceptable carrier.

[0057] For parenteral administration the formulation comprises a compound of the formula 1 and a physiologically acceptable diluent such as deionized water, physiological saline, 5% dextrose and other commonly used diluents. The formulation may contain a solubilizing agent such as a polyethylene glycol or polypropylene glycol or other known solubilizing agent. Such formulations may be made up in sterile vials containing the antifungal and excipient in a dry powder or lyophilized powder form. Prior to use, the physiologically acceptable diluent is added and the solution withdrawn via syringe for administration to the patient. For oral administration, the antifungal compound is filled into gelatin capsules or formed into tablets. Such tablets also contain a binding agent, a dispersant or other suitable excipients suitable for preparing a proper size tablet for the dosage and particular antifungal compound of the formula 1. For pediatric or geriatric use the antifungal compound may be formulated into a flavored liquid suspension, solution or emulsion. A preferred oral carrier system is lineolic acid, cremophor RH-60 and water and preferably in the amount (by volume) of 8% lineolic acid, 5% cremophor RH-60, and 87% sterile water. The compound is added to the system in an amount of 2.5 to 40 mg/ml.

[0058] For topical use the antifungal compound can be formulated with a dry powder for application to the skin surface or it may be formulated in a liquid formulation comprising a solubilizing aqueous liquid or non-aqueous liquid, e.g., an alcohol or glycol. Such formulations are useful forms for use in the antifungal method provided herein.

[0059] The N-acylcyclohexapeptides provided herein may be formulated as described above in unit dosage formulations comprising for injection between about 50 mg and about 500 mg per vial. For oral use gelatin capsules or tablets comprising between about 100 mg and about 500 mg per capsule or tablet can be provided.

[0060] Preferred formulations of the invention comprises the active ingredient presented by the formula 1 wherein R'=R"= methyl, R₁ is hydrogen and R₂ is 4-[4-(phenylethynyl)-phenyl]benzoyl in gelatin capsules or as active ingredient the antifungal represented by the formula 1 wherein R'=R"= methyl, R₁ is hydrogen and R₂ is 4-[4-[2-(4-cyclohexyl-piperidino)ethoxy]phenyl]benzoyl or the hydrochloride salt form thereof in tablet or gelatin capsules. Further preferred formulations are those in which a preferred compound, as described above, is employed.

[0061] In yet a further aspect of the present invention there is provided a method for treating patients suffering from Pneumocystis pneumonia. The method can be used prophylactically to prevent the onset of the infection which is caused by the organism Pneumocystis carinii. The N-acylcyclicpeptide can be administered parenterally, e.g. via intramuscular (i.m), intravenous (iv.) or intraperitoneal (i.p.) injection, or orally or by inhalation directly into the airways of the lungs. Preferably the cyclic peptide is administered via inhalation of an aerosol spray formulation of the compound.

[0062] An effective amount of a cyclic peptide will be between about 3 mg/kg of patient body weight to about 100 mg/kg. The amount administered may be in a single daily dose or multiple doses e.g. two, three or four times daily throughout the treatment regimen. The amount of the individual doses, the route of delivery, the frequency of dosing and the term of therapy will vary according to such factors as the intensity and extent of infection, the age and general health of the patient, the response of the patient to therapy and how well the patient tolerates the drug. It is known that PCP infections in AIDS patients are highly refractory owing to the nature of the infection. For example, in severe, advanced infections the luminal surface of the air passages becomes clogged with infectious matter and extensive parasite development occurs in lung tissue. A patient with an advanced infection will accordingly require higher doses for longer periods of time. In contrast, immune deficient patients who are not severely infected and who are susceptible to PCP can be treated with lower and less frequent prophylactic doses.

[0063] The activity of the cyclicpeptide represented by the formula 1 is demonstrated in immunosuppressed rats. The tests were carried out in general as follows. One week after initiation of immunosuppression rats were inoculated intratracheally with parasites and maintained on immunosuppression for the remainder of the study. Prophylactic treatments began one day after parasite inoculation and therapeutic treatments began 3 or 4 weeks later after moderate PCP developed. Eight or ten animals were assigned to the following groups: those receiving test compound; non-treated Pneumocystis infected control animals; animals treated with trimethoprim-sulfamethoxazole (TMP-SMX); or non-treated, non-infected control animals. The efficacy of different treatments was evaluated by monitoring animal weights and survival during the studies and by determining the severity of PCP at necropsy. Stained impression smears of the lungs and stained lung homogenates were evaluated to determine the intensity of P. carinii infection.

[0064] The immune deficient rats employed in the tests were prepared as follows. Female Lewis rats weighing from

120-140 g each were immune suppressed with methyl prednisolone acetate at a dose of 4 mg/100 g for the first week, 3 mg/100 g for the second week and continuing weekly thereafter at 2 mg/100 g. All rats, except for the non-infected control rats, were inoculated intratracheally with 0.1 ml to 0.2 ml of Dulbecco's Modified Eagle Media containing between >10⁵ and 10⁶ *P. carinii* (trophozoites, precysts and cysts) harvested from the lungs of heavily infected donor animals (infection scores of 6) and maintained as cryopreserved (liquid nitrogen) inocula. Rats were maintained on immune suppression and PCP was allowed to develop for 3 or 4 weeks before initiation of therapy with test compounds. Body weights were recorded weekly and rats were allocated into treatment groups such that each group had a similar distribution of percent weight loss among animals. Rats were treated with test compounds for 2 or 3 weeks and then were necropsied. For prophylaxis studies, administration of test compound was initiated one day after intratracheal inoculation of parasites and was continued until the rats were necropsied.

5 [0065] Following the evaluation period for test compounds, the rats were necropsied and test results evaluated by Giemsa-stained, silver-methenamine stained impression smears and/or by silver-methenamine stained lung homogenate (see below). Necropsy was carried out as follows. The test rats were anesthetized with a mixture of ketamine hydrochloride and xylazine and then exsanguinated via the right atrium. Internal organs in the abdominal and thoracic 10 cavities were examined for gross lesions.

15 [0066] A small portion of lung tissue from the left lobe of each rat was used to make the impression smears described below. Giemsa-stained impression smears were evaluated to determine the total number of parasites (trophozoites, precysts, and cysts). Impression smears from rats in groups whose treatments exhibited some anti-*Pneumocystis* activity (as judged by infection scores from Giemsa-stained slides) and from rats in the control groups were also stained 20 with methenamine silver, a stain specific for the cyst wall of the organism. Impression smears were randomized, numbered, and then evaluated. The infection scores used were as follows:

Score	Basis
0	No parasites found
1	1 to 5 parasites/10 oil fields
2	ca 1 parasite/field
3	2-10 parasites/field
4	>10 but <100 parasites/field
5	>100 but <1,000 parasites/field

25 A score of 6 was reserved for those infections with impression smears containing >1,000 organisms/field (too numerous to count). Giemsa-stained slides were examined microscopically using a final magnification of 1008X. Methenamine silver-stained slides were examined with a final magnification of 400X.

35 [0067] Cysts in rat lung tissue were quantified as follows. A small portion of lung tissue from the left lobe of each rat was used to make impression smears as described above. The remainder of each lung was weighed, placed in a tube containing Hanks balanced salt solution (HBSS) (40X the lung weight) and homogenized using a Brinkman model tissue homogenizer. Two μ l samples of the homogenized lung samples (1:4 dilution in HBSS) were placed in wells of teflon-coated, 12-well slides, stained with methenamine silver, and the number of cysts were scored as described 40 above for the impression smears.

45 [0068] The activity and efficacy of a preferred N-acylcyclohexapeptide in the test animals is presented below. The compound of the formula 1 wherein R'=R''= methyl, R₁ is hydrogen and R₂ is 4[(4-phenylethynyl)phenyl]benzoyl when administered as an aerosol solution at a concentration of 5 mg/ml for one hour, twice weekly for 5 weeks resulted in 90% reduction in *P. carinii* cysts in the lungs. When given orally at 10 mg/kg, bid for 3 weeks, the number of cysts in the lungs was reduced by >99% when compared with infected vehicle controls.

50 [0069] When the preferred N-acylcyclicpeptides were administered orally and by intraperitoneal injection the compound was effective in clearing *P. carinii* cysts from the lungs of heavily infected rats. For example, when the compound was administered at 10 or 40 mg/kg, bid for 4, 8 or 12 days, the number of identifiable cysts in the lungs of heavily infected rats was reduced by >99%. Similar efficacy was observed when the compound was administered i.p. at 1 mg/kg.

[0070] When tested orally for prophylactic activity, the preferred compound exhibited >99% cyst reduction in one of two studies when infected animals were dosed at 1 mg/kg and when given higher doses of 5 or 4 mg/kg.

55 [0071] The following examples of compounds of the invention and the manner of their preparation further describe the present invention.

N-Acylation of Cyclohexapeptide Nuclei

[0072] The preparation of the derivatives of the A30912A nucleus was accomplished by the following general procedure, with Table 27 listing these derivatives.

- 5 [0073] The A30912A nucleus and the 2,4,5-trichlorophenol ester are dissolved in dimethylformamide (25-50 ml) and stirred for 17-65 hours at room temperature. The solvent is removed *in vacuo* and the residue is slurried in ether and collected by filtration. The solid product is washed with methylene chloride and then dissolved in either methanol or acetonitrile/water (1:1 v/v). This solution is injected on a waters 600E semi-preparative chromatography system using a Rainin Dynamax-60A C₁₈ reverse-phase column. The column is eluted beginning with 20-40% aqueous acetonitrile and 0.5% monobasic ammonium phosphate (w/v) (monitored by UV at 230 nm and at a flow rate of 20 ml/min) until the unreacted A30912A nucleus is eluted and then deleting the buffer and eluting the product peak in aqueous acetonitrile. The fraction containing the product is evaporated *in vacuo* or lyophilized to provide the pure compound. The product may be analyzed by the same HPLC instrument using a Waters C₁₈ Micro Bondapak column and eluting with 40% aqueous acetonitrile containing 0.5% monobasic ammonium phosphate (w/v) at a 2 ml/min flow rate and monitoring the UV at 230 nm. The products may also be analyzed by fast atom bombardment mass spectrometry (FABMS). (In the compounds used, R'=R''=R'''=CH₃, R=OH, R'_Y=OH, R₁=H, R₇=OH, and R₂ is as defined).
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TABLE 27 continued

R ₂	Ester Reactant (mg)	A30912A Nucleus (P)	Product (mg)	FABMS	HPLC Retention (min)
	596	1.0	190	1078**	6.30
	571	1.0	295	1058**	7.91
	501	1.0	218	1002**	2.53

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[0074] Compounds such as those listed in Table 27 could be further modified at the phenolic hydroxy to provide R₇ = -OPO₃HNa as shown in Table 28. The procedure is as follows:

[0075] The lipopeptide (1 equivalent) and tetrabenzylpyrophosphate (2 equivalents) were dissolved in dimethylformamide which had been dried over 13X molecular sieves. Lithium hydroxide monohydrate (5 equivalents) was added and the stirred solution was monitored by HPLC. After 0.5 hr and 1 hr more lithium hydroxide (5 equivalents) was added. Between 1 and 2 hrs. the reaction was quenched with glacial acetic acid, the solvent removed under vacuum, and the residue purified over a semi-preparative C18 reverse-phase column using an aqueous acetonitrile eluent. The purified product was dissolved in (1/1) acetic acid/water with sodium acetate (1 equivalent) and 10% Pd/C catalyst.

TABLE 27 continued

R2	Ester Reactant(mg)	A30912A Nucleus (B)	Product (mg)	FABMS	HPLC Retention(min)
	566		1.0	81	1054* * 3.89

* (m-1)+[Na]⁺; ** (m+1); *** m+[Na]⁺

The solution was placed under an atmosphere of hydrogen gas and stirred for 1 hr. After filtering to remove the catalyst, the solution was lyophilized to provide the pure final product. The purity was assessed by analytical HPLC and the product was analyzed by fast atom bombardment mass spectrometry (FABMS).

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TABLE 28

R ₂	Start. Mat.	Wt. (mg)	Prod. R ₇	Wt. (mg)	FABMS
H ₃ C(CH ₂) ₃ O	-OII	300	-OPPO ₃ HNa	62	1228.4472*
* m+1					

Preparation of dideoxy cyclohexapeptide

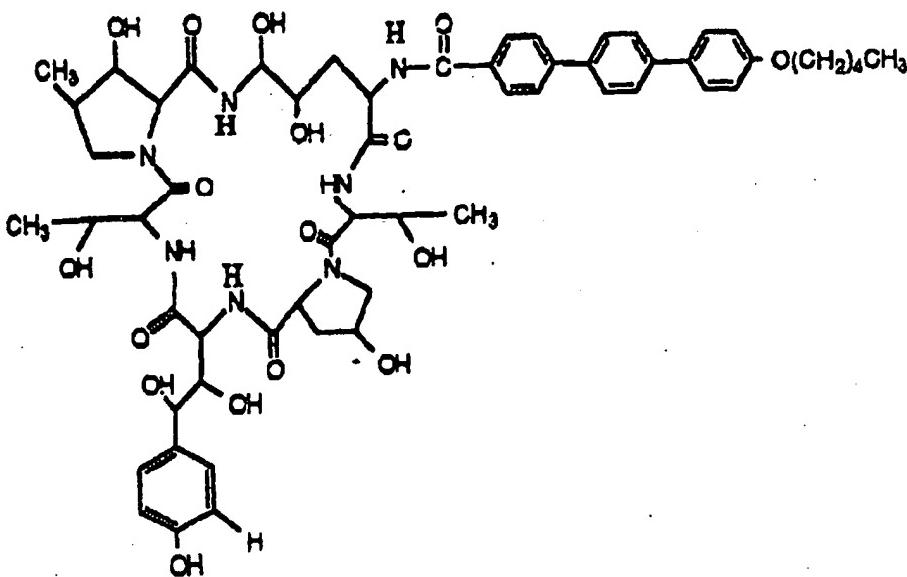
[0076] The preparation of the dideoxy compounds may be accomplished by the following procedure.

[0077] To a suspension of a non-dideoxy cyclohexapeptide (formula (I) where R=OH and R₂ is hydrogen or acyl), in dichloromethane is added the reducing agent triethylsilane in dichloromethane. The solution is stirred and the volatile components are removed under reduced pressure and the residue triturated with diethyl ether. The compound is purified using HPLC, and the product lyophilized.

ExampleDideoxcilofungin

[0078] To a suspension of cilofungin (10.00 g, 9.71 mmol) in dichloromethane (100 ml) was added a solution of triethylsilane (96 ml, 602 mmol) in dichloromethane (50 ml). Trifluoroacetic acid (46.4 ml, 602 mmol) was added as a solution in dichloromethane (50 ml) over 15 minutes. The solution was stirred at room temperature for two hours. The volatile reaction components were removed under reduced pressure and the residue triturated with diethyl ether. The compound was purified by reversed phase HPLC by means of a "Prep LC/System 500" unit (Waters Associates, Inc., Milford, Mass.) using a Prep Pak 500/C₁₈ Column (Waters Associates, Inc.) as the stationary phase. The column eluted with a gradient mobile phase using CH₃CN/H₂O (10:90 to 20:80 v/v) at 500 psi. The product containing fractions were pooled, evaporated under reduced pressure, and lyophilized from p-dioxane to yield dideoxcilofungin (6.66 g, 68.7%). FAB-MS: m/z calc. for C₄₉H₇₂N₇O₁₅, 998.5086; found, 998.512; UVλ(EtOH)nm(ε) 202.60(61012), 256.20(18569).

[0079] A compound of the formula

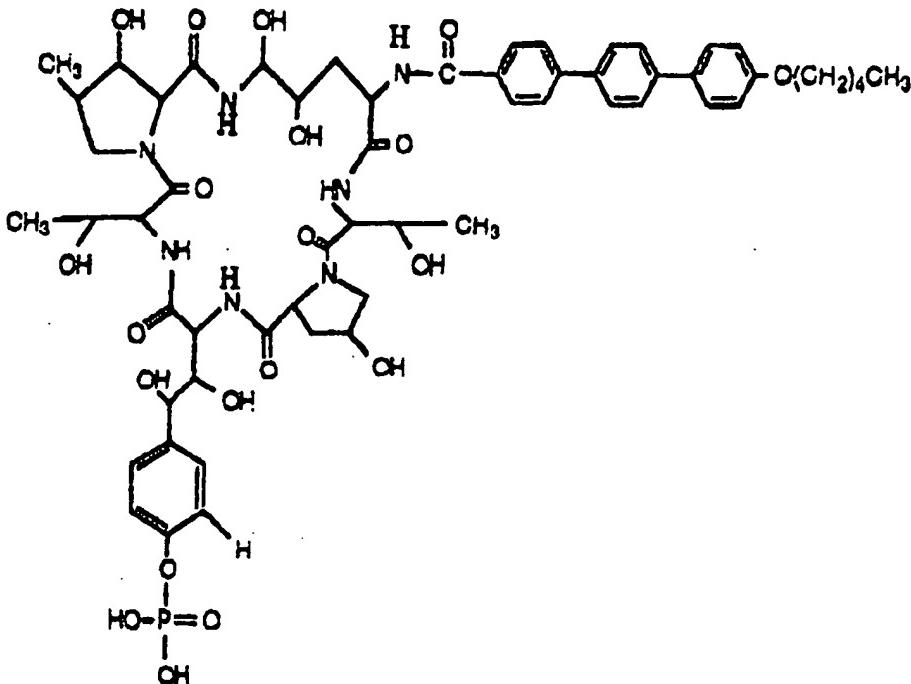


the preparation of which is discussed just prior to Table 27, can also be further modified at the phenolic hydroxy to provide R₇=-OPO₃HNa, as indicated in the two paragraphs prior to Table 28. The compound produced is as follows:

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The product was analyzed by FABMS (using Lit) to give a peak at 1226.4853 (calculated for C₅₈H₇₄N₇O₂₀PLi=1226.4886). Also, when analyzed by HPLC using a C18 reverse-phase column and eluting with 55% aqueous acetonitrile with 0.5% acetic acid at 2 ml/min and monitoring by UV at 280 nm, the compound had a retention time of 1.72 min.

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Claims

1. A compound of the formula (1):

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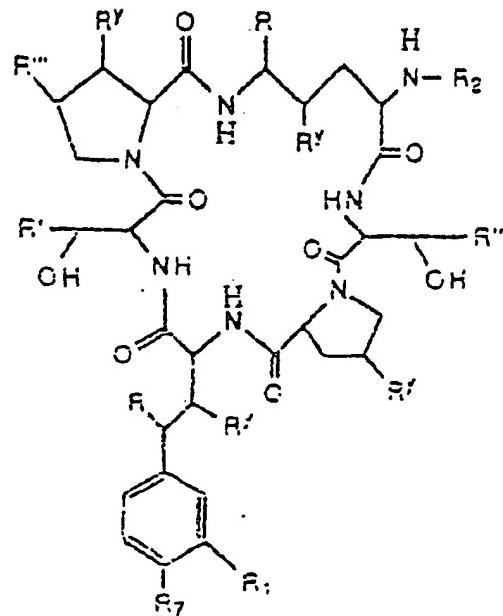
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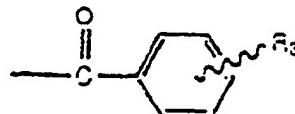
(1)



wherein

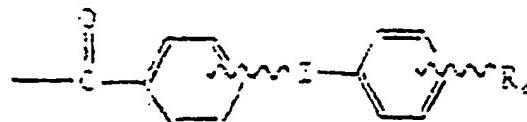
- R' is hydrogen, methyl or $\text{NH}_2\text{C}(\text{O})\text{CH}_2$;
- R'' and R''' are independently methyl or hydrogen;
- R and R^Y are independently hydroxy or hydrogen;
- R₁ is hydroxy, hydrogen or hydroxysulfonyloxy;
- R₇ is hydroxy, hydrogen, hydroxysulfonyloxy or phosphonoxy; and

I) R₂ is a substituted benzoyl group represented by the formula



wherein R₃ is quinolyl; or

(II) R₂ is an acyl group represented by the formula

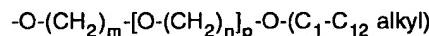


wherein

Z is -C≡C-, -CH=CH-, or a carbon to carbon bond;

(A) R₄ is C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, C₃-C₁₂ cycloalkoxy, naphthyl, pyridyl, thienyl, benzothienyl, quinolyl or phenyl; or

(B) R₄ is phenyl substituted by amino, C₁-C₁₂ alkylthio, halogen, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₁-C₁₂ substituted alkyl, C₂-C₁₂ substituted alkenyl, C₂-C₁₂ substituted alkynyl, C₁-C₁₂ alkoxy, trifluoromethyl, phenyl, substituted phenyl, phenyl substituted with a polyoxa-alkyl group represented by the formula



wherein m and n are integers of from 2 to 4, and p is 0 or 1; or

C) R₄ is phenyl substituted with C₁-C₆ alkoxy substituted by fluoro, bromo, chloro or iodo; or

D) R₄ is a group represented by the formula



wherein

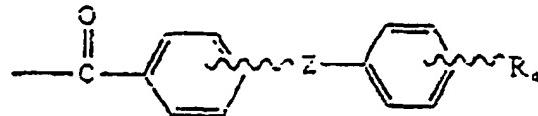
Y is -C≡C- or -C=C-; and

R₆ is C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyl; C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, phenyl, C₃-C₁₂ cycloalkenyl, naphthyl, benzothiazolyl, thienyl, phenyl substituted by amino, C₁-C₁₂ alkylthio, halogen, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₁-C₁₂ alkoxy, trifluoromethyl, -O-(CH₂)_p-W-R₅ wherein p' is an integer of from 2 to 4; W is pyrrolidino, piperidino or piperazino, and R₅ is hydrogen, C₁-C₁₂ alkyl, C₃-C₁₂ cycloalkyl, benzyl or C₃-C₁₂ cycloalkylmethyl; or C₁-C₆ alkoxy substituted by fluoro, bromo, iodo or chloro; or

R₆ is a phenyl substituted by a polyoxa-alkyl group represented by the formula

-O-(CH₂)_m-[O-(CH₂)_n]_p-O-(C₁-C₁₂ alkyl)

5 wherein m, n and p are as defined above; or
R₂ is an acyl group represented by the formula



wherein

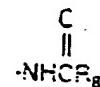
15 Z is -C≡C- or -CH=CH-;

- A) R₄ is hydrogen, C₂-C₁₂ alkynyl, C₂-C₁₂ substituted alkynyl, C₁-C₁₂ alkoxy; or
B) R₄ is C₁-C₁₂ alkoxy substituted with C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, C₂-C₁₂
20 alkynyl, amino, C₁-C₄ alkylamino, di-(C₁-C₄ alkyl)amino, C₁-C₁₂ alkanoylamino, phenyl substituted with
a polyoxa-alkyl group represented by the formula

-O-(CH₂)_m-[O-(CH₂)_n]_p-O-(C₁-C₁₂ alkyl)

25 wherein m, n and p are as defined; or

C) R₄ is C₁-C₁₂ alkoxy substituted with a group of the formula



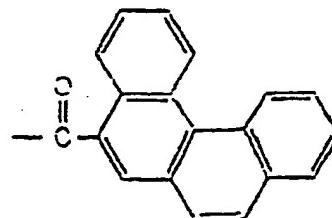
wherein R₃ is C₁-C₆ alkoxy optionally substituted with phenyl; or

35 D) R₄ is a group represented by the formula

-O-(CH₂)_{p'}-W-R₅

40 wherein p', W and R₅ are as defined; or

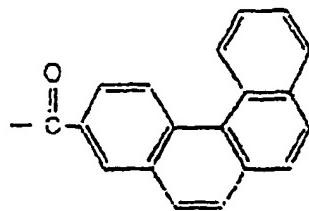
IV) R₂ is a group having the formula



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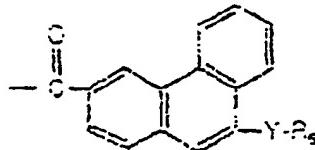
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wherein Y and R₆ are as defined above; or
20 V) R₂ is naphthoyl substituted with R₄

wherein

- 25 A) R₄ is C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, C₃-C₁₂ cycloalkoxy, naphthyl, pyridyl, thiienyl, benzothienyl, quinolyl or phenyl; or
B) R₄ is phenyl substituted by amino, C₁-C₁₂ alkylthio, halogen, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₁-C₁₂ substituted alkyl, C₂-C₁₂ substituted alkenyl, C₂-C₁₂ substituted alkynyl, C₁-C₁₂ alkoxy, trifluoromethyl, phenyl, substituted phenyl, phenyl substituted with a polyoxa-alkyl group represented by the formula

30 -O-(CH₂)_m-[O-(CH₂)_n]_p-O-(C₁-C₁₂ alkyl)

wherein m, n and p are as defined; or

- 35 C) R₄ is phenyl substituted with C₁-C₆ alkoxy substituted by fluoro, bromo, chloro or iodo; or
D) R₄ is a group represented by the formula

-Y-R₆

40 wherein Y has the same meanings as defined above; and

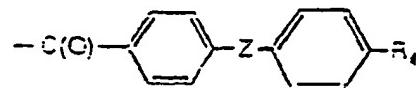
R₆ is C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyl; C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, phenyl, C₃-C₁₂ cycloalkenyl, naphthyl, benzothiazolyl, thiienyl, phenyl substituted by amino, C₁-C₁₂ alkylthio, halogen, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₁-C₁₂ alkoxy, trifluoromethyl, -O-(CH₂)_p-W-R₅, or C₁-C₆ alkoxy substituted by fluoro, bromo, iodo or chloro; or

45 R₆ is a phenyl substituted by a polyoxa-alkyl group represented by the formula

-O-(CH₂)_m-[O-(CH₂)_n]_p-O-(C₁-C₁₂ alkyl)

50 wherein m, n and p are as defined above; and the pharmaceutically acceptable non-toxic salts thereof.

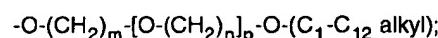
2. A compound according to claim 1 wherein R₁ is hydroxy or hydrogen and R₇ is hydroxy or hydrogen.
- 55 3. A compound according to claim 1 or claim 2 wherein R', R'' and R''' are methyl, R₁ is hydrogen, and R₇ and R₈ are OH.
4. A compound according to any one of claims 1 to 3 wherein R₂ is of the formula



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wherein

Z is a carbon to carbon bond; and

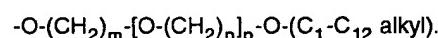
R₄ is C₃-C₇ cycloalkoxy; or10 R₄ is phenyl substituted by C₁-C₁₂ alkoxy or phenyl substituted with a polyoxa-alkyl group of the formula

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or

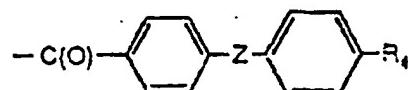
R₄ is a group of the formula -Y-R₆, wherein Y is -C≡C- or -C=C- and R₆ is C₁-C₆ alkyl, phenyl, or phenyl substituted with a polyoxa-alkyl group of the formula

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5. A compound according to any one of claims 1 to 3 wherein R₂ is of the formula

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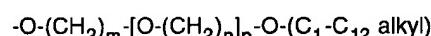
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wherein

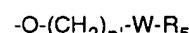
Z is -C≡C-; and

R₄ is phenyl substituted by C₁-C₁₂ alkoxy or phenyl substituted with a polyoxa-alkyl group of the formula

35



or

40 R₄ is a group of the formula

wherein W is a piperidine group.

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6. A compound according to any one of claims 1 to 3 wherein R is hydrogen.

7. A compound according to any one of claims 1 to 3 wherein R₂ is 4-[4-(phenylethynyl)phenyl]benzoyl or 4-[4-(n-butylethynyl)phenyl]beraoyl.

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8. A compound of the formula (1):

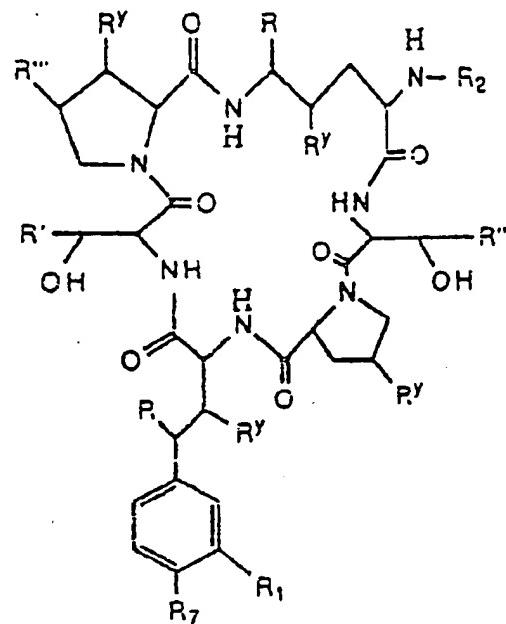
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wherein

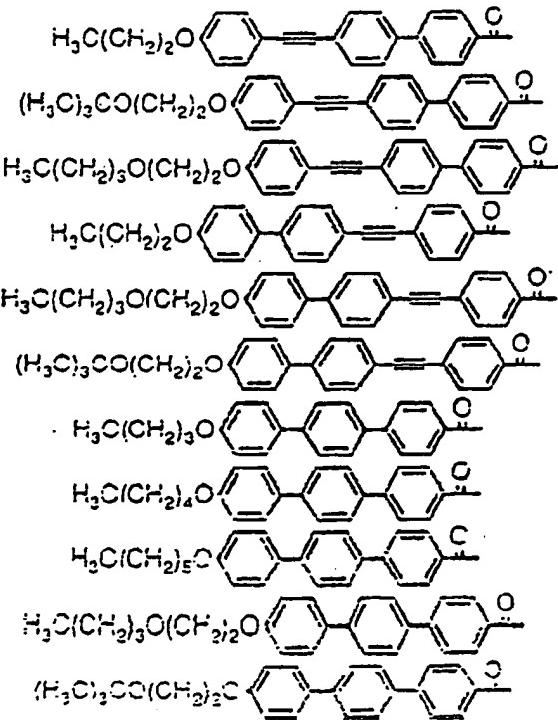
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R' is hydrogen, methyl or $\text{NH}_2\text{C}(\text{O})\text{CH}_2$;
 R'' and R''' are independently methyl or hydrogen;
 R and R γ are independently hydroxy or hydrogen;
 R₁ is hydroxy, hydrogen, or hydroxysulfonyloxy;
 R₇ is hydroxy, hydrogen, hydroxysulfonyloxy or phosphonoxy; and

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I) R₂ is a group of the formula

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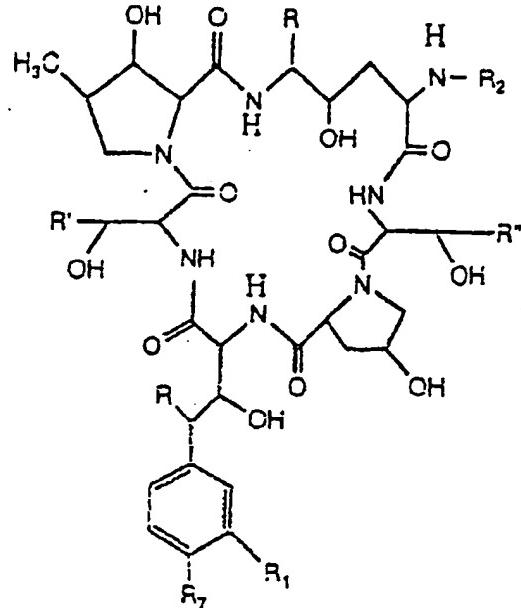
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and pharmaceutically acceptable salts thereof.

9. A compound according to claim 8 wherein R', R" and R''' are methyl, R₁ is hydrogen and R₇ and R_Y are hydroxy.

5 10. A compound of the formula (1):



wherein

30 R' is hydrogen, methyl or NH₂C(O)CH₂-;

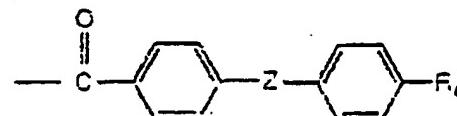
R" is methyl or hydrogen;

R is hydroxy or hydrogen;

R₁ is hydroxy, hydrogen, or hydroxysulfonyloxy;

35 R₇ is hydroxy, hydrogen, hydroxysulfonyloxy or phosphonoxy;

R₂ is an acyl group represented by the formula



wherein Z is -C=C-, -CH=CH-, or a carbon to carbon bond;

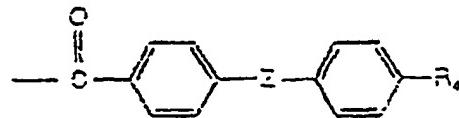
45 R₄ is C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, phenyl, phenyl substituted by amino, C₁-C₁₂ alkythio, halogen, C₁-C₁₂ alkyl, C₁-C₁₂ alkoxy, trifluoromethyl, phenyl, or C₁-C₆ alkoxy substituted by fluoro, bromo, chloro or iodo;

or R₄ is C₃-C₁₂ cycloalkoxy;

50 or R₄ is a group represented by the formula -Y-R₆ wherein Y is -C=C- or -CH=CH- and R₆ is C₁-C₁₂ alkyl, C₁-C₁₂ alkyl substituted by phenyl; C₃-C₁₂ cycloalkyl, phenyl, C₃-C₁₂ cycloalkenyl, naphthyl, benzthiazol-2-yl, or phenyl substituted by amino, C₁-C₁₂ alkythio, halogen, C₁-C₁₂ alkyl, C₁-C₁₂ alkenyl, C₁-C₁₂ alkoxy, trifluoromethyl, -O-(CH₂)_p-W-R₅ wherein p' is an integer of from 2 to 4; W is pyrrolidino, piperidino or piperazino, and R₅ is hydrogen, C₁-C₁₂ alkyl, C₃-C₁₂ cycloalkyl, benzyl or C₃-C₁₂ cycloalkylmethyl; or C₁-C₆ alkoxy substituted by fluoro, bromo, iodo or chloro;

55 or R₂ is an acyl group represented by the formula

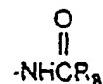
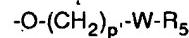
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wherein

10 Z is $-\text{C}\equiv\text{C}-$ or $-\text{CH}=\text{CH}-$; R_4 is hydrogen:R₄ is C₁-C₁₂ alkoxy, C₁-C₁₂ alkoxy substituted by C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, amino, C₁-C₄ alkylamino, di-(C₁-C₄ alkyl)amino, C₁-C₁₂ alkanoylamino or a group of the formula

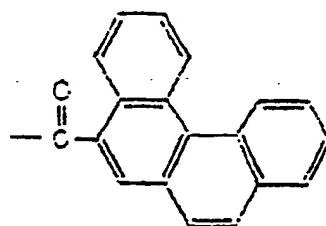
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20 wherein R_8 is C₁-C₆ alkoxy optionally substituted with phenyl; or R_4 is a group represented by the formula

25 or

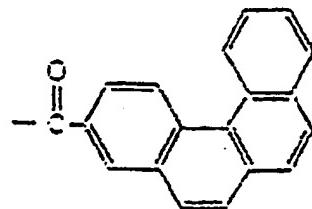
 R_2 is a group selected from

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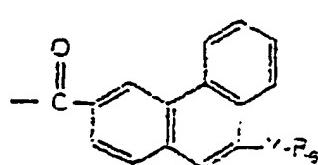
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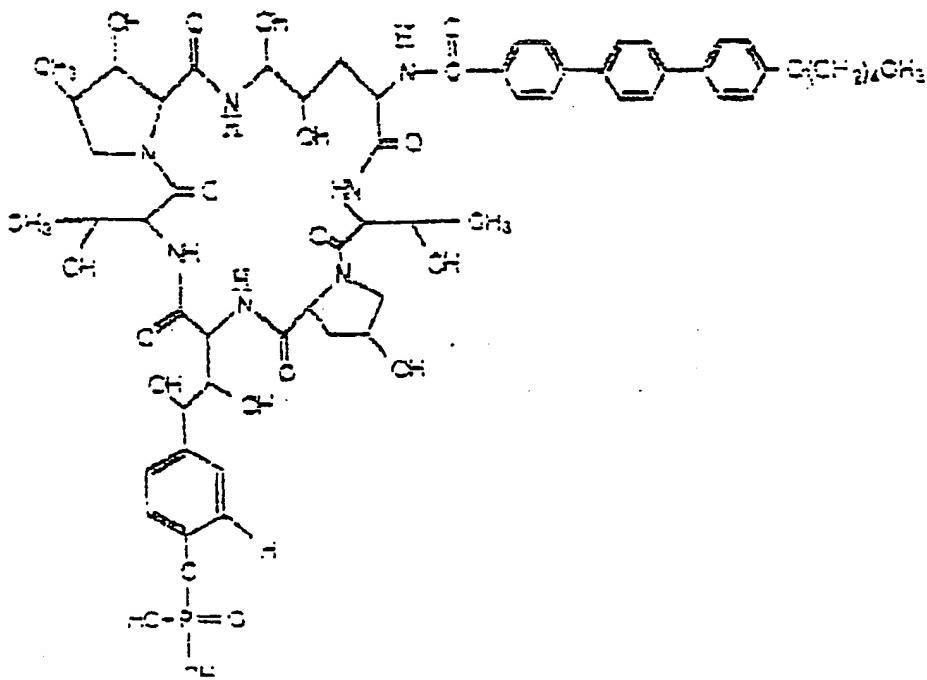
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wherein

Y and R₆ are as defined above; or
 R₂ is naphthoyl substituted with R₄ wherein
 R₄ is C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, phenyl, phenyl substituted by amino, C₁-C₁₂ alkythio, halogen, C₁-C₁₂ alkyl, C₁-C₁₂ alkoxy, trifluoromethyl, phenyl, or C₁-C₆ alkoxy substituted by fluoro, bromo, chloro or iodo;
 or R₄ is C₃-C₁₂ cycloalkoxy;
 or R₄ is a group represented by the formula -Y-R₆ wherein Y has the same meanings as defined above and R₆ is C₁-C₁₂ alkyl, C₁-C₁₂ alkyl substituted by phenyl; C₃-C₁₂ cycloalkyl, phenyl, C₃-C₁₂ cycloalkenyl, naphthyl, benzthiazol-2-yl, or phenyl substituted by amino, C₁-C₁₂ alkythio, halogen, C₁-C₁₂ alkyl, C₁-C₁₂ alkenyl, C₁-C₁₂ alkoxy, trifluoromethyl, -O-(CH₂)_p-W-R₅, or C₁-C₆ alkoxy substituted by fluoro, bromo, iodo or chloro; and the pharmaceutically acceptable non-toxic salts thereof.

11. A compound according to claim 10 wherein R₁ is not hydroxysulfonyloxy and R₇ is not hydroxysulfonyloxy or phosphonoxy.

15 12. A compound of the formula

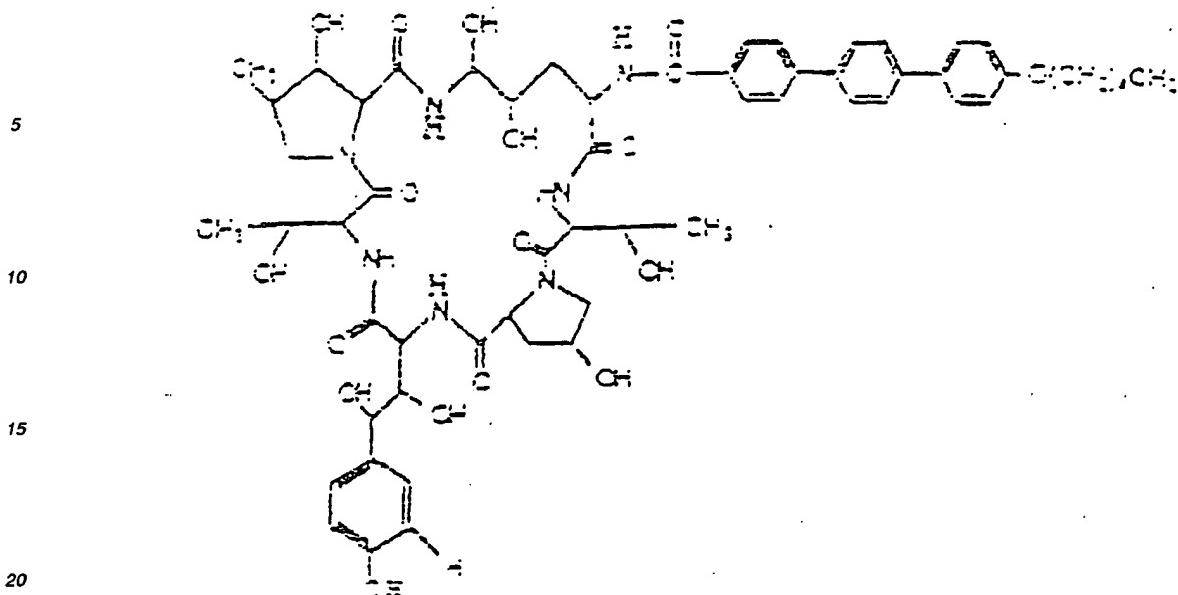


13. A compound of the formula

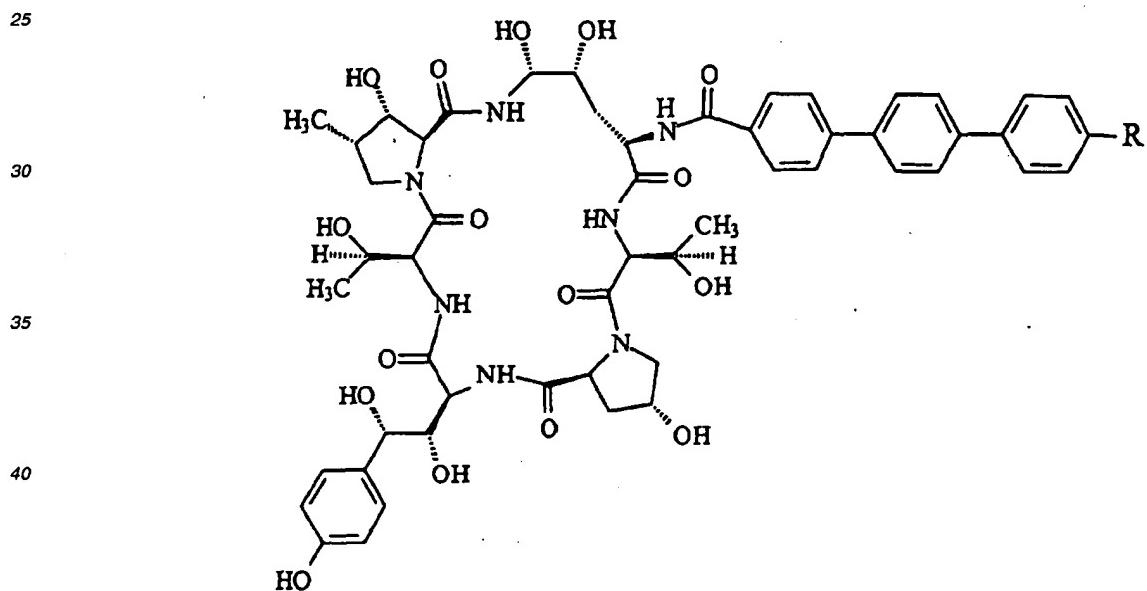
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14. A compound of the formula



wherein R is -O(CH₂)₃CH₃, -O(CH₂)₄CH₃, -O(CH₂)₅CH₃, -O(CH₂)₂O(CH₂)₃CH₃ or -O(CH₂)₂OC(CH₃)₃.

15. A compound according to claim 14 wherein R is -O(CH₂)₄CH₃.

16. A compound according to any of claims 1-15 for use in inhibiting parasitic activity.

17. A compound according to any one of claims 1-15 for use in inhibiting fungal activity.

18. A compound according to any of claims 1-15 for use in inhibiting the growth of organisms responsible for opportunistic infections in immunosuppressed individuals.

19. A compound according to any of claims 1-15 for use in inhibiting the growth of Pneumocystis carinii.

20. A pharmaceutical formulation comprising a compound according to any of claims 1-15 and a suitable pharmaceutical carrier.

21. A process for the preparation of a compound of the formula (1):

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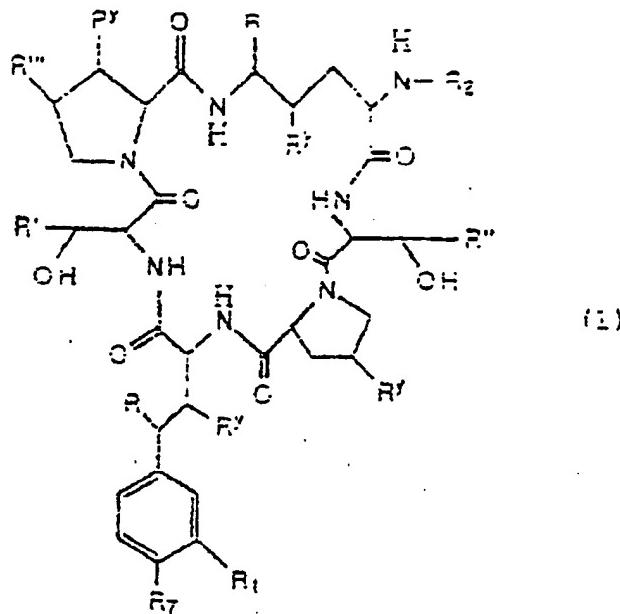
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wherein

R' is hydrogen, methyl or $\text{NH}_2\text{C}(\text{O})\text{CH}_2$;

R'' and R''' is methyl or hydrogen;

R is hydrogen;

Ry is hydroxy or hydrogen;

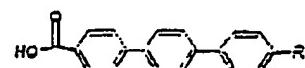
R₁ is hydroxy, or hydrogen;

R₇ is hydroxy, or hydrogen; and

R₂ is hydrogen or acyl;

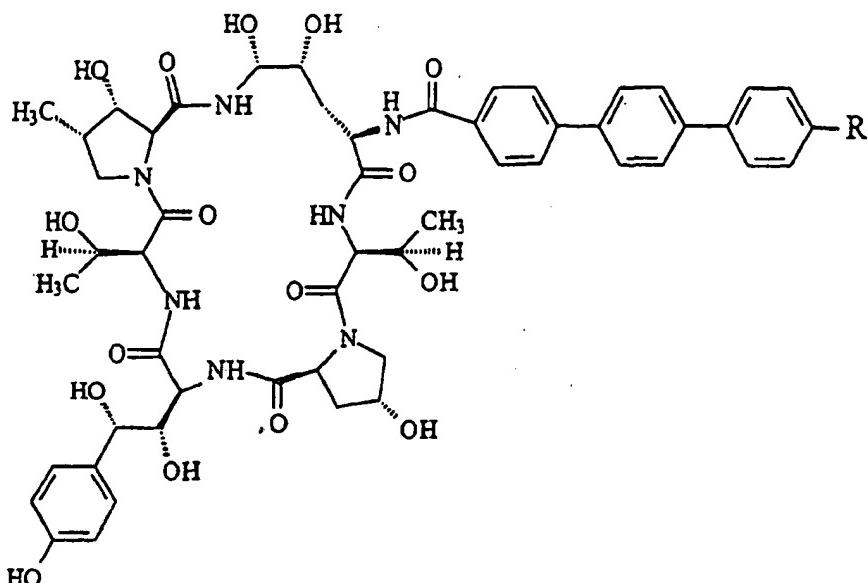
comprising the step of subjecting a compound of formula (1) wherein R=OH, to a strong acid in the presence of a reducing agent, in a suitable solvent.

22. A process for producing an N-acyl cyclic hexapeptide which process comprises acylating an amino nucleus of Echinocandin B with an active ester of a carboxylic acid represented by the formula



wherein R is $-\text{O}(\text{CH}_2)_3\text{CH}_3$, $-\text{O}(\text{CH}_2)_4\text{CH}_3$, $-\text{O}(\text{CH}_2)_5\text{CH}_3$, $-\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CH}_3$ or $-\text{O}(\text{CH}_2)_2\text{OC}(\text{CH}_3)_3$.

23. A process for preparing a compound of the formula



wherein R is -O(CH₂)₃CH₃, -O(CH₂)₄CH₃, -O(CH₂)₅CH₃, -O(CH₂)₂O(CH₂)₃CH₃ or -O(CH₂)₂OC(CH₃)₃ which process comprises acylating an amino nucleus of Echinocandin B with an active ester of a carboxylic acid represented by the formula



24. A process according to claim 22 or claim 23 wherein R is
$$-\text{O}(\text{CH}_2)_4\text{CH}_3.$$

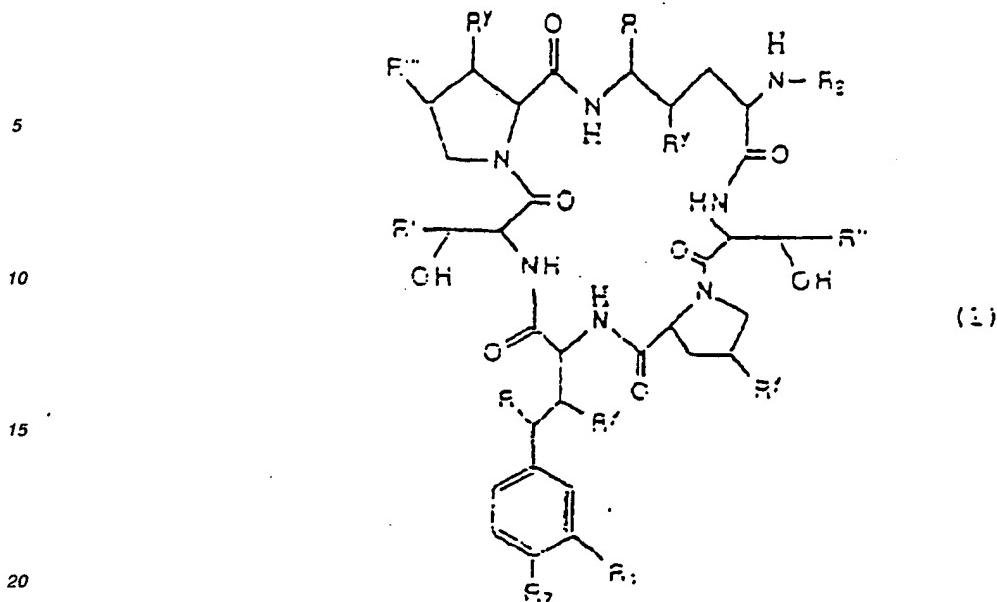
25. A process according to any one of claims 22-24 wherein the active ester is a 2,4,5-trichlorophenyl ester.

26. A process according to any one of claims 22-25 wherein the amine nucleus of Echinocandin B is obtained by N-deacylation of a naturally occurring cyclic hexapeptide.

27. A process according to claims 26 wherein the naturally occurring cyclic hexapeptide is echinocandin B, tetrahydroechinocandin B, mulundocandin, L-671 329, S 31794/FI, sporiofungin or FR 901379.

Patentansprüche

- #### 1. Verbindungen der Formel (1):



worin

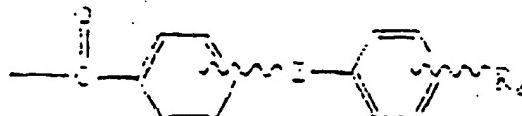
- 25 R' Wasserstoff, Methyl oder $\text{NH}_2\text{C(O)CH}_2$ - ist;
R" und R'" unabhängig voneinander Methyl oder Wasserstoff sind;
R und R γ unabhängig voneinander Hydroxy oder Wasserstoff sind;
R₁ Hydroxy, Wasserstoff oder Hydroxysulfonyloxy ist;
R₇ Hydroxy, Wasserstoff, Hydroxysulfonyloxy oder Phosphonoxy ist; und

30 I) R₂ eine substituierte Benzoylgruppe der Formel



ist, worin R₃ Chinolyl ist; oder

- II) R₂ eine Acylgruppe der Formel



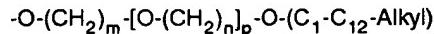
ist, worin

- 50 Z-C≡C-; -CH=CH-, oder eine Kohlenstoff-zu-Kohlenstoff-Bindung ist;

55 (A) R₄C₃-C₁₂-Cycloalkyl, C₇-C₁₀-Bicycloalkyl, C₇-C₁₄ Tricycloalkyl, C₃-C₁₂-Cycloalkoxy, Naphthyl, Pyridyl, Thienyl, Benzothienyl, Chinolyl oder Phenyl ist; oder

(B) R₄ Phenyl, substituiert durch Amino, C₁-C₁₂-Alkylthio, Halogen, C₁-C₁₂-Alkyl, C₂-C₁₂-Alkenyl, C₂-C₁₂-Alkynyl, substituiertes C₁-C₁₂-Alkyl, substituiertes C₂-C₁₂-Alkenyl, substituiertes C₂-C₁₂-Alkynyl, C₁-C₁₂-Alkoxy, Trifluormethyl, Phenyl, substituiertes Phenyl, Phenyl, substituiert mit einer Polyoxa-Alkylgruppe

der Formel



5

worin m und n ganze Zahlen von 2 bis 4 sind und p 0 oder 1 ist; oder

(C) R₄ Phenyl, substituiert mit C₁-C₆-Alkoxy, substituiert durch Fluor, Brom, Chlor oder Iod, ist; oder

10

(D) R₄ eine Gruppe der Formel



15

ist, worin

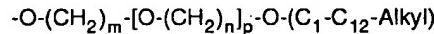
Y -C≡C- oder -C=C-, ist; und

20

R₆C₁-C₁₂-Alkyl, substituiertes C₁-C₁₂-Alkyl; C₃-C₁₂-Cycloalkyl, C₇-C₁₀-Bicycloalkyl, C₇-C₁₄-Tricycloalkyl, Phenyl, C₃-C₁₂-Cycloalkenyl, Naphthyl, Benzothiazolyl, Thienyl, Phenyl, substituiert durch Amino, C₁-C₁₂-Alkylthio, Halogen, C₁-C₁₂-Alkyl, C₂-C₁₂-Alkenyl, C₂-C₁₂-Alkynyl, C₁-C₁₂-Alkoxy, Trifluormethyl, -O-(CH₂)_p-W-R₅, worin p eine ganze Zahl von 2 bis 4 ist, W Pyrrolidino, Piperidino oder Piperazino ist, ist, und R₅ Wasserstoff, C₁-C₁₂-Alkyl, C₃-C₁₂-Cycloalkyl, Benzyl oder C₃-C₁₂-Cycloalkylmethoxy ist; oder C₁-C₆-Alkoxy, substituiert durch Fluor, Brom, Iod oder Chlor, ist; oder

25

R₆ ein Phenyl, substituiert durch eine Polyoxa-Alkylgruppe der Formel

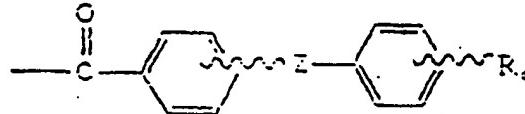


30

ist, worin m, n und p wie oben definiert sind, oder

R₂ eine Acylgruppe der Formel

35



40

ist, worin

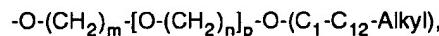
Z -C≡C- oder -CH=CH- ist;

45

A) R₄ Wasserstoff, C₂-C₁₂-Alkynyl, substituiertes C₂-C₁₂-Alkynyl, C₁-C₁₂-Alkoxy ist; oder

B) R₄ C₁-C₁₂-Alkoxy, substituiert durch C₃-C₁₂-Cycloalkyl, C₇-C₁₀-Bicycloalkyl, C₇-C₁₄-Tricycloalkyl, C₂-C₁₂-Alkynyl, Amino, C₁-C₄-Alkylamino, Di-(C₁-C₄-alkyl)amino, C₁-C₁₂-Alkanoylamino, Phenyl, substituiert mit einer Polyoxa-Alkylgruppe der Formel

50



55

worin m, n und p wie definiert sind, ist; oder

C) R₄ C₁-C₁₂-Alkoxy, substituiert mit einer Gruppe der Formel

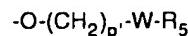
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worin R_8 C_1 - C_6 -Alkoxy, gegebenenfalls substituiert mit Phenyl ist; oder

D) R_4 eine Gruppe der Formel



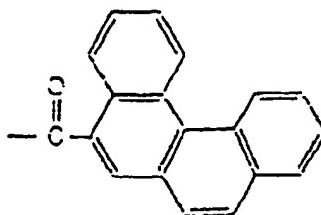
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ist, worin p' , W und R_5 wie definiert sind; oder

15

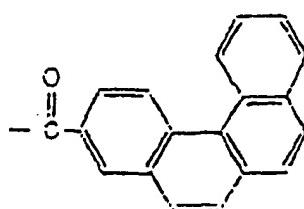
IV) R_2 eine Gruppe der Formel

20



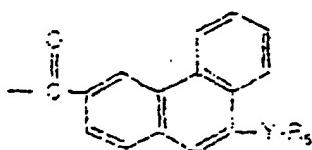
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ist, worin Y und R_6 wie oben definiert sind; oder

V) R_2 Naphthoyl ist, substituiert mit R_4 , worin

50

(A) R_4 C_3 - C_{12} -Cycloalkyl, C_7 - C_{10} -Bicycloalkyl, C_7 - C_{14} Tricycloalkyl, C_3 - C_{12} -Cycloalkoxy, Naphthyl, Pyridyl, Thienyl, Benzothienyl, Chinolyl oder Phenyl ist; oder

55

(B) R_4 Phenyl, substituiert durch Amino, C_1 - C_{12} -Alkylthio, Halogen, C_1 - C_{12} -Alkyl, C_2 - C_{12} -Alkenyl, C_2 - C_{12} -Alkynyl, substituiertes C_1 - C_{12} -Alkyl, substituiertes C_2 - C_{12} -Alkenyl, substituiertes C_2 - C_{12} -Alkynyl, C_1 - C_{12} -Alkoxy, Trifluormethyl, Phenyl, substituiertes Phenyl, Phenyl, substituiert mit einer Polyoxa-Alkylgruppe der Formel

$-\text{O}-(\text{CH}_2)_m-\text{[O}-(\text{CH}_2)_n\text{]}_p-\text{O}-(\text{C}_1\text{-C}_{12}\text{-Alkyl}),$

worin m, n und p wie definiert sind, ist; oder

5

(C) R_4 Phenyl, substituiert mit $\text{C}_1\text{-C}_6$ -Alkoxy, substituiert durch Fluor, Brom, Chlor oder Iod, ist; oder

(D) R_4 eine Gruppe der Formel

10

$-\text{Y-R}_6$

ist, worin

15

Y die gleichen Bedeutungen wie oben definiert besitzt; und

20

$\text{R}_6 \text{C}_1\text{-C}_{12}\text{-Alkyl}$, substituiertes $\text{C}_1\text{-C}_{12}\text{-Alkyl}$; $\text{C}_3\text{-C}_{12}\text{-Cycloalkyl}$, $\text{C}_7\text{-C}_{10}\text{-Bicycloalkyl}$, $\text{C}_7\text{-C}_{14}\text{-Tricycloalkyl}$, Phenyl, $\text{C}_3\text{-C}_{12}\text{-Cycloalkenyl}$, Naphthyl, Benzothiazolyl, Thienyl, Phenyl, substituiert durch Amino, $\text{C}_1\text{-C}_{12}\text{-Alkylthio}$, Halogen, $\text{C}_1\text{-C}_{12}\text{-Alkyl}$, $\text{C}_2\text{-C}_{12}\text{-Alkenyl}$, $\text{C}_2\text{-C}_{12}\text{-Alkynyl}$, $\text{C}_1\text{-C}_{12}\text{-Alkoxy}$, Trifluormethyl, $-\text{O}-(\text{CH}_2)_p-\text{W-R}_5$, oder $\text{C}_1\text{-C}_6\text{-Alkoxy}$, substituiert durch Fluor, Brom, Iod oder Chlor, ist; oder

R_6 ein Phenyl, substituiert durch eine Polyoxa-Alkylgruppe der Formel

25

$-\text{O}-(\text{CH}_2)_m-\text{[O}-(\text{CH}_2)_n\text{]}_p-\text{O}-(\text{C}_1\text{-C}_{12}\text{-Alkyl})$

ist, worin m, n und p wie oben definiert sind; und pharmazeutisch zulässige nichttoxische Salze davon.

30

2. Verbindung nach Anspruch 1, worin R_1 Hydroxy oder Wasserstoff ist und R_7 Hydroxy oder Wasserstoff ist.

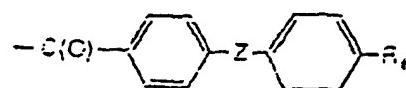
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3. Verbindung gemäß Anspruch 1 oder Anspruch 2, worin R' , R'' und R''' Methyl sind, R_1 Wasserstoff ist und R_7 und R' OH sind.

40

4. Verbindung gemäß mindestens einem der Ansprüche 1 bis 3, worin R_2 von folgender Formel ist

35



45

worin

Z eine Kohlenstoff-zu-Kohlenstoff-Bindung ist; und

$\text{R}_4 \text{C}_3\text{-C}_7\text{-Cycloalkoxy}$ ist; oder

45

R_4 Phenyl, substituiert durch $\text{C}_1\text{-C}_{12}\text{-Alkoxy}$, oder Phenyl, substituiert mit einer Polyoxa-Alkylgruppe der Formel

50

$-\text{O}-(\text{CH}_2)_m-\text{[O}-(\text{CH}_2)_n\text{]}_p-\text{O}-(\text{C}_1\text{-C}_{12}\text{-Alkyl}),$

ist; oder

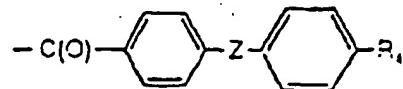
R_4 eine Gruppe der Formel $-\text{Y-R}_6$ ist, worin Y $-\text{C}\equiv\text{C}-$ oder $-\text{C}=\text{C}-$ ist, und $\text{R}_6 \text{C}_1\text{-C}_6\text{-Alkyl}$, Phenyl oder Phenyl, substituiert mit einer Polyoxa-Alkylgruppe der Formel

55

$-\text{O}-(\text{CH}_2)_m-\text{[O}-(\text{CH}_2)_n\text{]}_p-\text{O}-(\text{C}_1\text{-C}_{12}\text{-Alkyl}),$

ist.

5. Verbindung gemäß mindestens einem der Ansprüche 1 bis 3, worin R₂ die Formel

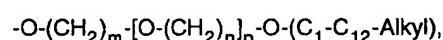


aufweist, worin

10 Z -C≡C- ist; und

R₄ Phenyl, substituiert durch C₁-C₁₂-Alkoxy- oder Phenyl, substituiert mit einer Polyoxa-Alkylgruppe der Formel

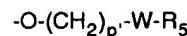
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ist,

oder R₄ eine Gruppe der Formel

20



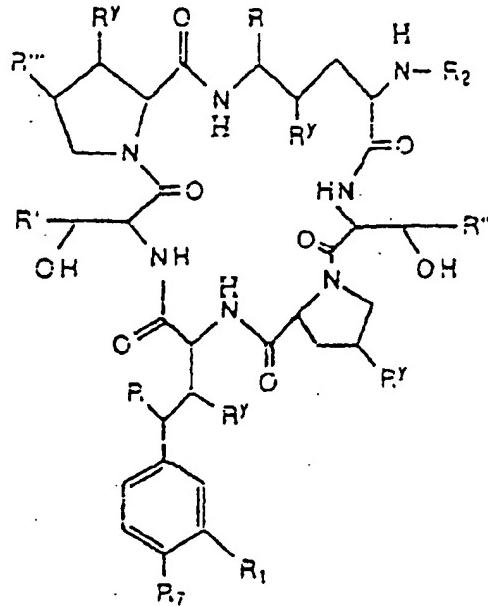
ist,

25 worin W eine Piperidingruppe ist.

6. Verbindung gemäß mindestens einem der Ansprüche 1 bis 3, worin R Wasserstoff ist.

7. Verbindung gemäß mindestens einem der Ansprüche 1 bis 3, worin R₂ 4-[4-(Phenylethynyl)phenyl]benzoyl oder
30 4-[4-(n-Butylethynyl)phenyl]benzoyl ist.

8. Verbindung der Formel (1):



45

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55

worin

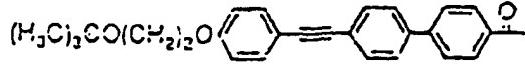
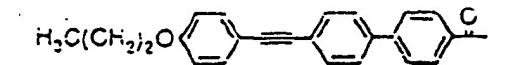
R' Wasserstoff, Methyl oder NH₂C(O)CH₂- ist;

R["] und R^{'''} unabhängig voneinander Methyl oder Wasserstoff sind;
 R und R^y unabhängig voneinander Hydroxy oder Wasserstoff sind;
 R₁ Hydroxy, Wasserstoff oder Hydroxysulfonyloxy ist;
 R₇ Hydroxy, Wasserstoff, Hydroxysulfonyloxy oder Phosphonoxy ist; und

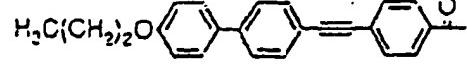
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I) R₂ eine Gruppe der Formel

10



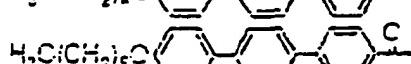
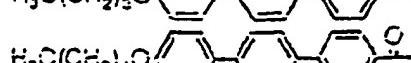
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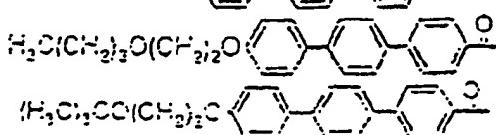
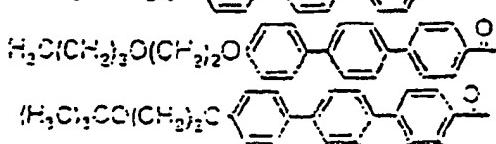
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ist, und pharmazeutisch annehmbare Salze davon.

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9. Verbindung gemäß Anspruch 8, worin R', R" und R''' Methyl sind, R₁ Wasserstoff ist und R₇ und R^y Hydroxy sind.

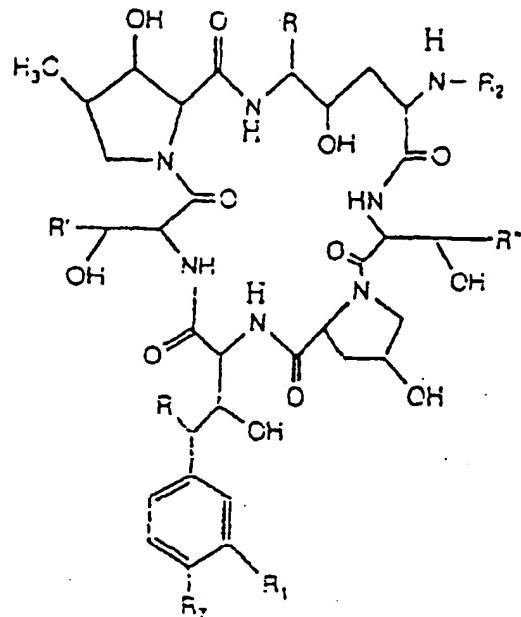
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10. Verbindung der Formel (1):

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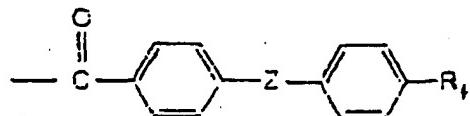


worin

25 R' Wasserstoff, Methyl oder $\text{NH}_2\text{C(O)CH}_2$ - ist;

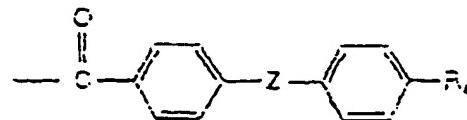
R'' Methyl oder Wasserstoff ist;

R Hydroxy oder Wasserstoff ist;

30 R₁ Hydroxy, Wasserstoff oder Hydroxysulfonyloxy ist;R₇ Hydroxy, Wasserstoff, Hydroxysulfonyloxy oder Phosphonoxy ist;35 R₂ eine Acylgruppe der Formel

ist, worin Z -C≡C-, -CH=CH- oder eine Kohlenstoff-zu-Kohlenstoff-Bindung ist;

45 R₄ C₃-C₁₂-Cycloalkyl, C₇-C₁₀-Bicycloalkyl, C₇-C₁₄-Tricycloalkyl, Phenyl, Phenyl, substituiert durch Amino, C₁-C₁₂-Alkylthio, Halogen, C₁-C₁₂-Alkyl, C₁-C₁₂-Alkoxy, Trifluormethyl, Phenyl oder C₁-C₆-Alkoxy, substituiert durch Fluor, Brom, Chlor oder Iod, ist;50 oder R₄ C₃-C₁₂-Cycloalkoxy ist;oder R₄ eine Gruppe der Formel -Y-R₆ ist, worin Y -C≡C- oder -CH=CH- ist, und R₆ C₁-C₁₂-Alkyl, C₁-C₁₂-Alkyl, substituiert durch Phenyl; C₃-C₁₂-Cycloalkyl, Phenyl, C₃-C₁₂-Cycloalkenyl, Naphthyl, Benzthiazol-2-yl oder Phenyl, substituiert durch Amino, C₁-C₁₂-Alkylthio, Halogen, C₁-C₁₂-Alkyl, C₁-C₁₂-Alkenyl, C₁-C₁₂-Alkoxy, Trifluormethyl, -O-(CH₂)_p-W-R₅, worin p' eine ganze Zahl von 2 bis 4 ist; W Pyrrolidino, Piperidino oder Piperazino ist, ist, und R₅ Wasserstoff, C₁-C₁₂-Alkyl, C₃-C₁₂-Cycloalkyl, Benzyl oder C₃-C₁₂-Cycloalkylmethyl ist; oder C₁-C₆-Alkoxy, substituiert durch Fluor, Brom, Iod oder Chlor, ist;oder R₂ eine Acylgruppe der Formel



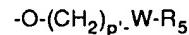
ist, worin Z -C≡C- oder -CH=CH- ist;

10 R₄ Wasserstoff ist;

R₄ C₁-C₁₂-Alkoxy, C₁-C₁₂-Alkoxy, substituiert durch C₃-C₁₂-Cycloalkyl, C₇-C₁₀-Bicycloalkyl, C₇-C₁₄-Tricycloalkyl, Amino, C₁-C₄-Alkylamino, Di-(C₁-C₄-alkyl)amino, C₁-C₁₂-Alkanoylamino oder eine Gruppe der Formel

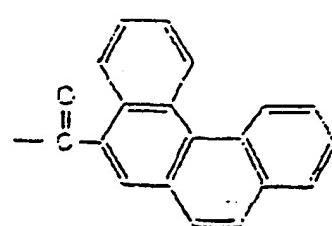


20 worin R₈ C₁-C₆-Alkoxy, optional substituiert mit Phenyl, ist; oder R₄ eine Gruppe der Formel

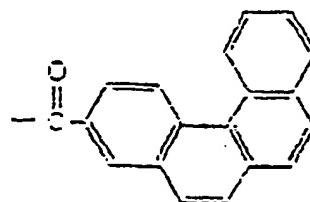


25 ist, oder

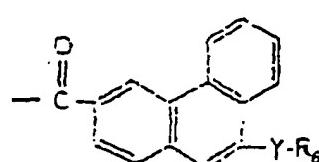
R₂ eine Gruppe ist, die aus



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gewählt ist, worin Y und R₆ wie oben definiert sind; oder

R₂ Naphthyl, substituiert mit R₄ ist, worin

R₄ C₃-C₁₂-Cycloalkyl, C₇-C₁₀-Bicycloalkyl, C₇-C₁₄-Tricycloalkyl, Phenyl, Phenyl, substituiert mit Amino, C₁-C₁₂-Alkylothio, Halogen, C₁-C₁₂-Alkyl, C₁-C₁₂-Alkoxy, Trifluormethyl, Phenyl oder C₁-C₆-Alkoxy, substituiert durch Fluor, Brom, Chlor oder Iod, ist;

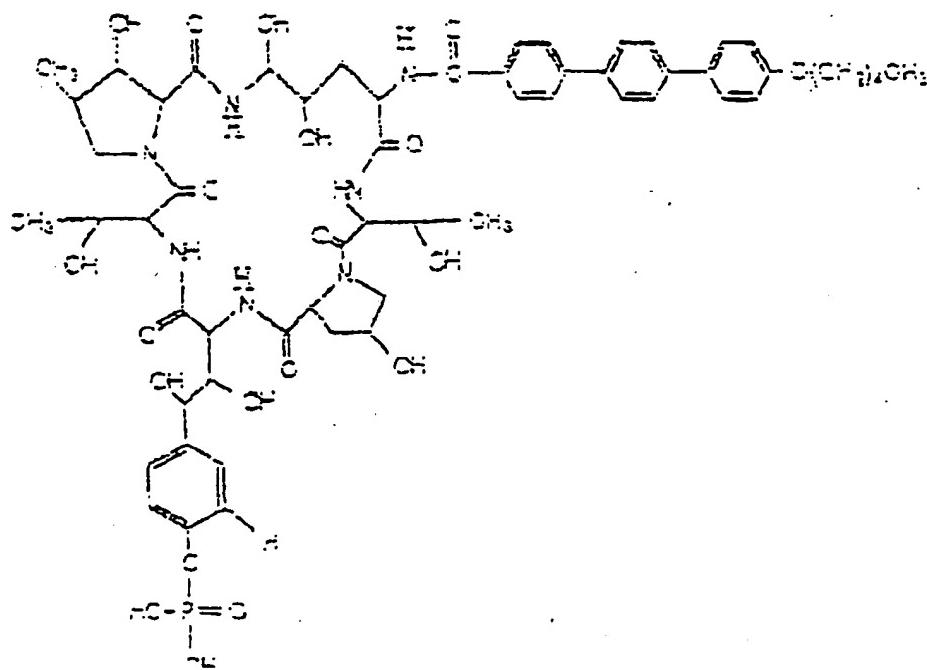
oder R₄ C₃-C₁₂-Cycloalkoxy ist;

oder R₄ eine Gruppe der Formel -Y-R₆ ist, worin Y die gleiche Bedeutung wie obenstehend besitzt, und R₆

C₁-C₁₂-Alkyl, C₁-C₁₂-Alkyl, substituiert durch Phenyl; C₃-C₁₂-Cycloalkyl, Phenyl, C₃-C₁₂-Cycloalkenyl, Naphthyl, Benzthiazol-2-yl oder Phenyl, substituiert durch Amino, C₁-C₁₂-Alkylothio, Halogen, C₁-C₁₂-Alkyl, C₁-C₁₂-Alkenyl, C₁-C₁₂-Alkoxy, Trifluormethyl, -O-(CH₂)_p-W-R₅ oder C₁-C₆-Alkoxy, substituiert durch Fluor, Brom, Iod oder Chlor, ist; und die pharmazeutisch annehmbaren nicht-toxischen Salze davon.

11. Verbindung gemäß Anspruch 10, worin R₁ nicht Hydroxysulfonyloxy ist und R₇ nicht Hydroxysulfonyloxy oder Phosphonoxy ist.

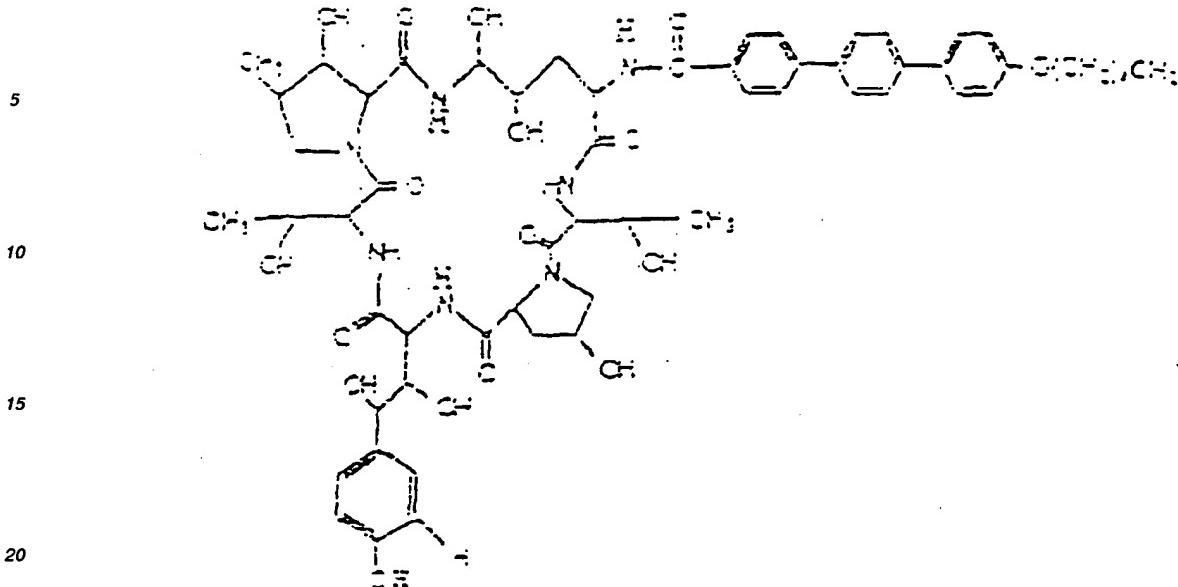
12. Verbindung der Formel



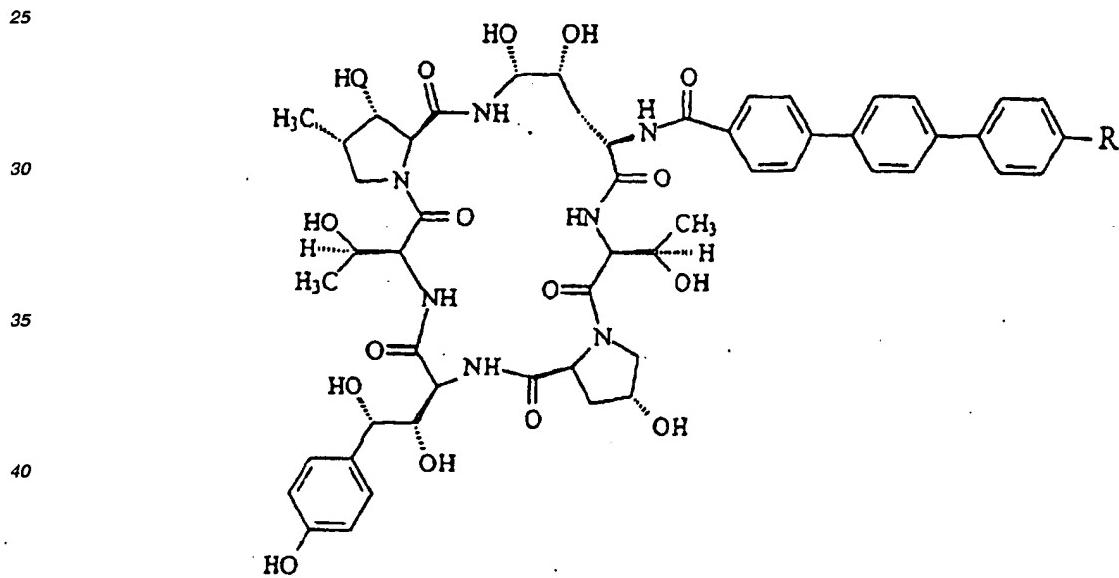
13. Verbindung der Formel

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14. Verbindung der Formel



worin R -O(CH₂)₃CH₃, -O(CH₂)₄CH₃, -O(CH₂)₅CH₃, -O(CH₂)₂O(CH₂)₃CH₃ oder -O(CH₂)₂OC(CH₃)₃ ist.

15. Verbindung gemäß Anspruch 14, worin R -O(CH₂)₄CH₃ ist.

16. Verbindung gemäß mindestens einem der Ansprüche 1-15 zur Verwendung bei der Inhibierung parasitischer Aktivität.

17. Verbindung gemäß mindestens einem der Ansprüche 1-15 zur Verwendung bei der Inhibierung fungaler Aktivität.

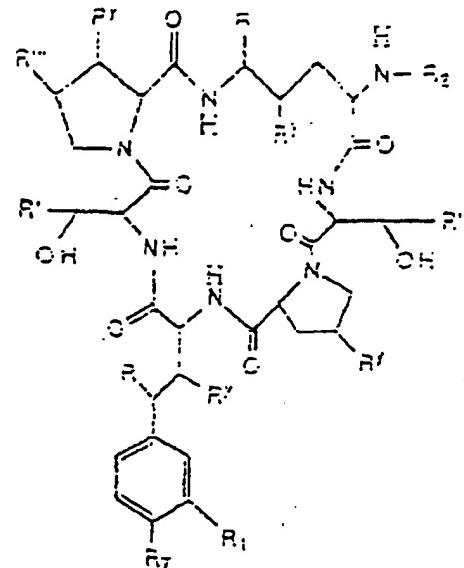
18. Verbindung gemäß mindestens einem der Ansprüche 1-15 zur Verwendung bei der Inhibierung des Wachstums von Organismen, die für opportunistische Infektionen bei Individuen mit Immunosuppression verantwortlich sind.

19. Verbindung gemäß mindestens einem der Ansprüche 1-15 zur Verwendung bei der Inhibierung des Wachstums von *Pneumocystis carinii*.

20. Pharmazeutische Formulierung, umfassend eine Verbindung gemäß mindestens einem der Ansprüche 1-15 und einen geeigneten pharmazeutischen Träger.

21. Verfahren zur Herstellung einer Verbindung der Formel (1):

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worin

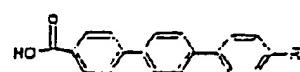
- 30 R' Wasserstoff, Methyl oder NH₂C(O)CH₂- ist;
 R" und R''' Methyl oder Wasserstoff ist;
 R Wasserstoff ist;
 R^y Hydroxy oder Wasserstoff ist;
 R₁ Hydroxy oder Wasserstoff ist;
 35 R₇ Hydroxy oder Wasserstoff ist; und
 R₂ Wasserstoff oder Acyl ist;

umfassend die Schritte des Unterziehens einer Verbindung der Formel (1), worin R=OH ist, einer starken Säure in Gegenwart eines Reduktionsmittels in einem geeigneten Lösungsmittel.

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22. Verfahren zur Herstellung von cyclischem N-Acyl-Hexapeptid, wobei das Verfahren das Acylieren eines Aminokerns von Echinocandin B mit einem aktiven Ester einer Carbonsäure der Formel

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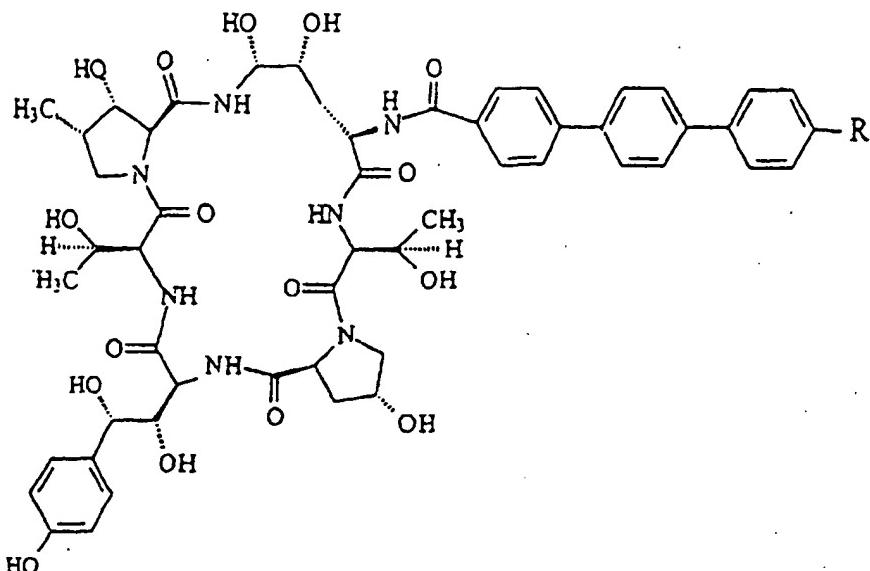
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umfasst, worin R -O(CH₂)₃CH₃, -O(CH₂)₄CH₃, -O(CH₂)₅CH₃, -O(CH₂)₂O(CH₂)₃CH₃ oder -O(CH₂)₂OC(CH₃)₃ ist.

23. Verfahren zur Herstellung einer Verbindung der Formel

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worin R -O(CH₂)₃CH₃, -O(CH₂)₄CH₃, -O(CH₂)₅CH₃, -O(CH₂)₂O(CH₂)₃CH₃ oder -O(CH₂)₂OC(CH₃)₃ ist, wobei das Verfahren die Acylierung eines Aminokerns von Echinocandin B mit einem aktiven Ester einer Carbonsäure der Formel

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30

umfasst.

24. Verfahren gemäß Anspruch 22 oder Anspruch 23, worin R -O(CH₂)₄CH₃ ist.

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25. Verfahren gemäß mindestens einem der Ansprüche 22-24, bei dem der aktive Ester ein 2,4,5-Trichlorphenylester ist.

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26. Verfahren gemäß mindestens einem der Ansprüche 22-25, bei dem der Aminkern von Echinocandin B erhalten wird durch die N-Deacylierung eines natürlich auftretenden cyclischen Hexapeptids.

27. Verfahren gemäß Anspruch 26, bei dem das natürlich auftretende cyclische Hexapeptid Echinocandin B, Tetrahydroechinocandin B, Mulundocandin, L-671 329, S 31794/FI, Sporofungin oder FR 901379 ist.

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Revendications

1. Composé de formule (1) :

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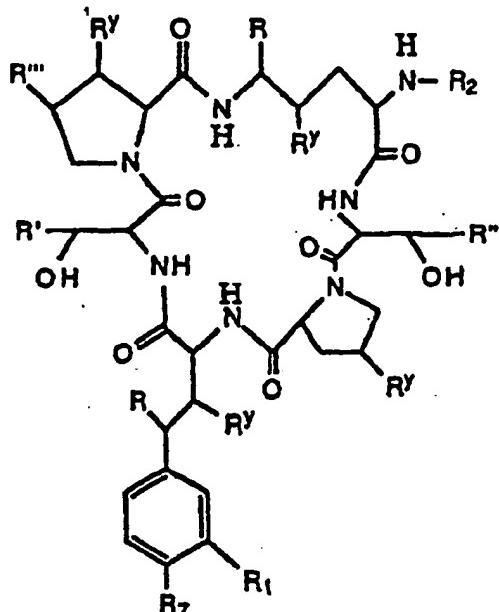
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(1)



dans laquelle

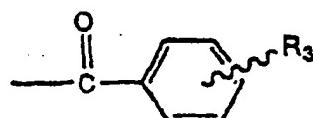
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R' est hydrogène, méthyle, ou $\text{NH}_2\text{C}(\text{O})\text{CH}_2^-$;
 R'' et R''' sont indépendamment méthyle ou hydrogène ;
 R et RY sont indépendamment hydroxy ou hydrogène ;
 R1 est hydroxy, hydrogène ou hydroxysulfonyloxy ;
 R7 est hydroxy, hydrogène, hydroxysulfonyloxy ou phosphonoxy ; et

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I) R2 est un groupe benzoyle substitué représenté par la formule

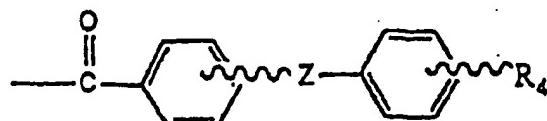
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dans laquelle R3 est quinolyle ; ou
 II) R2 est un groupe acyle représenté par la formule

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dans laquelle

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Z est $-\text{C}\equiv\text{C}-$, $-\text{CH}=\text{CH}-$ ou une liaison carbone-carbone ;

A) R4 est un groupe cycloalkyle en C3 à C12, bicycloalkyle en C7 à C10, tricycloalkyle en C7 à C14, cycloalcoxy en C3 à C12, naphtyle, pyridyle, thiényle, benzothiényle, quinolyle ou phényle ; ou

B) R4 est un groupe phényle substitué par un groupe amino, alkylthio en C1 à C12, halogène, alkyle en C1 à C12, alcényle en C2 à C12, alcynyle en C2 à C12, alkyle en C1 à C12 substitué, alcényle en C2 à C12 substitué, alcynyle en C2 à C12 substitué, alcoxy en C1 à C12, trifluorométhyle, phényle, phényle substitué, phényle substitué par un groupe polyoxa-alkyle représenté par la formule

-O-(CH₂)_m-[O-(CH₂)_n]_p-O-(alkyle en C₁ à C₁₂)

dans laquelle m et n sont des entiers de 2 à 4, et p est 0 ou 1 ; ou

5 C) R₄ est un groupe phényle substitué par un alcoxy en C₁ à C₆ substitué par fluoro, bromo, chloro ou iodo ; ou

D) R₄ est un groupe représenté par la formule

10 -Y-R₆

dans laquelle

15 Y est -C≡C- ou -CH=CH- ; et

R₆ est un alkyle en C₁ à C₁₂, alkyle substitué en C₁ à C₁₂; cycloalkyle en C₃ à C₁₂, bicycloalkyle en C₇ à C₁₀, tricycloalkyle en C₇ à C₁₄, phényle, cycloalcényle en C₃ à C₁₂, naphtyle, benzothiazolyle, thiényle, phényle substitué par amino, alkylthio en C₁ à C₁₂, halogène, alcényle en C₂ à C₁₂, alcyne en C₂ à C₁₂, alcoxy en C₁ à C₁₂, trifluorométhyle, -O-(CH₂)_p-W-R₅, dans lequel p' est un entier de 2 à 4 ; W est pyrrolidino, pipéridino ou pipérazino, et R₅ est un hydrogène, alkyle en C₁ à C₁₂, cycloalkyle en C₃ à C₁₂, benzyle ou cycloalkylméthyle en C₃ à C₁₂; ou alcoxy en C₁ à C₆ substitué par fluoro, bromo, iodo ou chloro ; ou

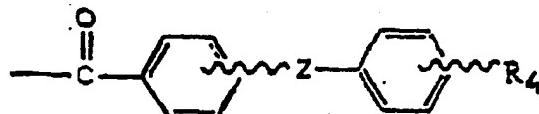
20 R₆ est un phényle substitué par un groupe polyoxa-alkyle représenté par la formule

25 -O-(CH₂)_m-[O-(CH₂)_n]_p-O-(alkyle en C₁ à C₁₂)

dans laquelle m, n et p sont tels que définis ci-dessus ; ou

30 III) R₂ est un groupe acyle représenté par la formule

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dans laquelle

40 Z est -C≡C- ou -CH=CH- ;

40

A) R₄ est un hydrogène, alcyne en C₂ à C₁₂, alcyne substitué en C₂ à C₁₂, alcoxy en C₂ à C₁₂; ou
B) R₄ est alcoxy en C₁ à C₁₂ substitué avec cycloalkyle en C₃ à C₁₂, bicycloalkyle en C₇ à C₁₀, tricycloalkyle en C₇ à C₁₄, alcyne en, amino, alkylamino en C₁ à C₄, di-(alkyle en C₁ à C₄)amino, alcanoyleamino en C₁ à C₁₂, phényle substitué par un groupe polyoxa-alkyle représenté par la formule

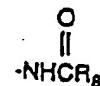
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-O-(CH₂)_m-[O-(CH₂)_n]_p-O-(alkyle en C₁ à C₁₂)

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dans laquelle m, n et p sont tels que définis ci-dessus ; ou

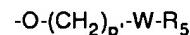
C) R₄ est un alcoxy substitué avec un groupe de formule



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dans laquelle R₈ est un alcoxy en C₁ à C₅ éventuellement substitué par un phényle ; ou

D) R₄ est un groupe représenté par la formule

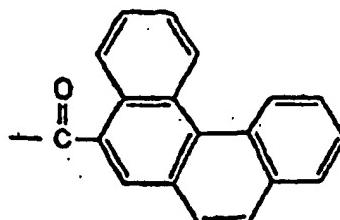


dans laquelle p' , W et R_5 sont tels que définis ; ou

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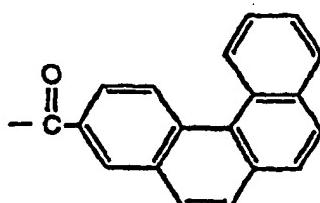
IV) R_2 est un groupe ayant la formule

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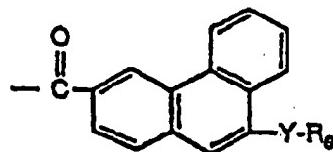
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dans laquelle Y et R_6 sont tels que définis ci-dessus ; ou

V) R_2 est un naphtoyle substitué par R_4

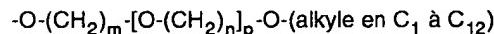
dans lequel

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A) R_4 est un cycloalkyle en C_3 à C_{12} , bicycloalkyle en C_7 à C_{10} , tricycloalkyle en C_7 à C_{14} , cycloalcoxy en C_3 à C_{12} , naphtyle, pyridyle, thiényle, benzothiényle, quinolyde ou phényle : ou

B) R_4 est un phényle substitué par un amino, alkylthio en C_1 à C_{12} , halogène, alkyle en C_1 à C_{12} , alcényle en C_2 à C_{12} , alcynyle en C_2 à C_{12} , alkyle substitué en C_1 à C_{12} , alcényle substitué en C_2 à C_{12} , alcynyle substitué en C_2 à C_{12} , alcoxy en C_1 à C_{12} , trifluorométhyle, phényle, phényle substitué, phényle substitué avec un groupe polyoxa-alkyle représenté par la formule

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dans laquelle m, n et p sont tels que définis ; ou

C) R_4 est un phényle substitué par un alcoxy en C_1 à C_6 substitué par un fluoro, bromo, chlore ou iodo ; ou

D) R_4 est un groupe représenté par la formule

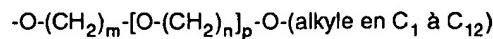
dans laquelle

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Y a les significations identiques telles que définies ci-dessus ; et

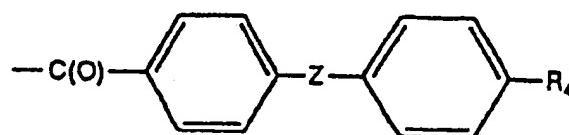
R_6 est un alkyle en C_1 à C_{12} , alkyle substitué en C_1 à C_{12} , cycloalkyle en C_3 à C_{12} , bicycloalkyle en C_7 à C_{10} , tricycloalkyle en C_7 à C_{14} , phényle, cycloalcényle en C_3 à C_{12} , naphtyle, benzothiazolyle, thiényle, phényle substitué par amino, alkylthio en C_1 à C_{12} , halogène, alcényle en C_2 à C_{12} , alcynyle en C_2 à C_{12} , alcoxy en C_1 à C_{12} , trifluorométhyle, $-\text{O}-(\text{CH}_2)_p-\text{W}-\text{R}_5$, ou alcoxy en C_1 à C_6 substitué

par fluoro, bromo, iodo ou chloro ; ou
 R₆ est un phényle substitué par un groupe polyoxa-alkyle représenté par la formule



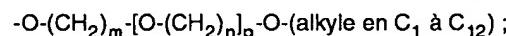
dans laquelle m, n et p sont tels que définis; et leurs sels non toxiques pharmaceutiquement acceptables.

- 10 2. Composé selon la revendication 1 dans lequel R₁ est hydroxy ou hydrogène et R₇ est hydroxy ou hydrogène.
 3. Composé selon la revendication 1 ou la revendication 2 dans lequel R', R'' et R''' sont un méthyle, R₁ est hydrogène, et R₇ et R''' sont OH.
 15 4. Composé selon l'une quelconque des revendications 1 à 3 dans lequel R₂ est de formule



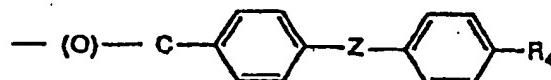
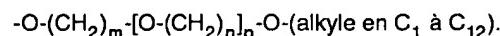
dans laquelle

25 Z est une liaison carbone-carbone; et
 R₄ est un cycloalcoxy en C₃ à C₇; ou
 R₄ est un phényle substitué par un alcoxy en C₁ à C₁₂ ou phényle substitué par un groupe polyoxa-alkyle de formule



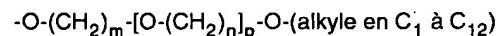
ou

35 R₄ est groupe de formule -Y-R₆, dans laquelle Y est -C≡C- ou -CH=CH- et R₆ est un alkyle en C₁ à C₆, phényle ou phényle substitué par un groupe polyoxa-alkyle de formule



dans laquelle

50 Z est -C≡C- ; et
 R₄ est un phényle substitué par un alcoxy en C₁ à C₁₂ ou phényle substitué par un groupe polyoxa-alkyle de formule



ou

R₄ est un groupe de formule

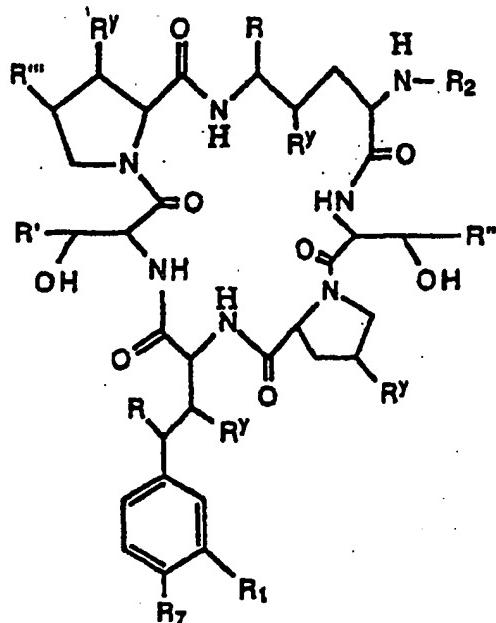
-O-(CH₂)_p-W-R₅

dans laquelle W est un groupe pipéridine.

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6. Composé selon l'une quelconque des revendications 1 à 3 dans lequel R est un hydrogène.
7. Composé selon l'une quelconque des revendications 1 à 3 dans lequel R₂ est 4-[4-(phényléthynyl)phényl]benzoyle ou 4-[4-(n-butyléthynyl)phényl]benzoyle.
- 10 8. Composé de formule (1) :

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dans laquelle

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R' est hydrogène, méthyle, ou NH₂C(O)CH₂⁻ ;
 R'' et R''' sont indépendamment méthyle ou hydrogène ;
 R et R^Y sont indépendamment hydroxy ou hydrogène ;
 R₁ est hydroxy, hydrogène ou hydroxsulfonyloxy ;
 R₇ est hydroxy, hydrogène, hydroxsulfonyloxy ou phosphonoxy ; et

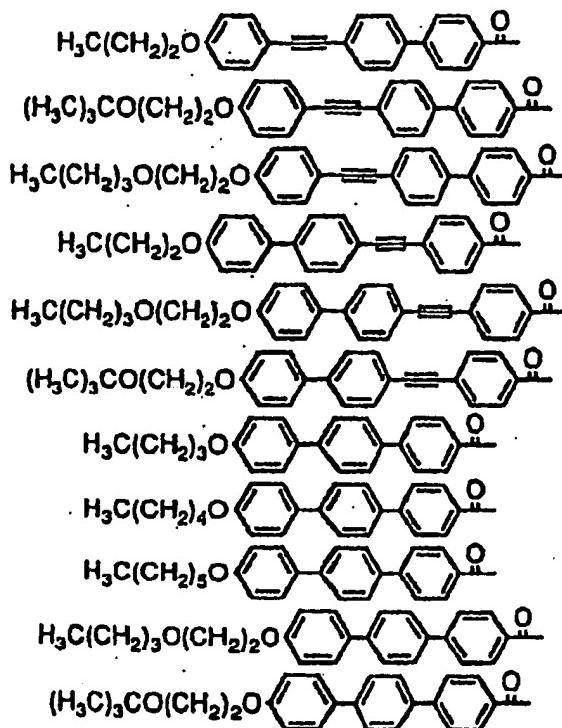
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I) R₂ est un groupe de formule

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et leurs sels pharmaceutiquement acceptables.

9. Composé selon la revendication 8 dans lequel R', R'' et R''' sont un méthyle, R₁ est un hydrogène et R₇ et R₈ sont hydroxy.

10. Composé de formule (1) :

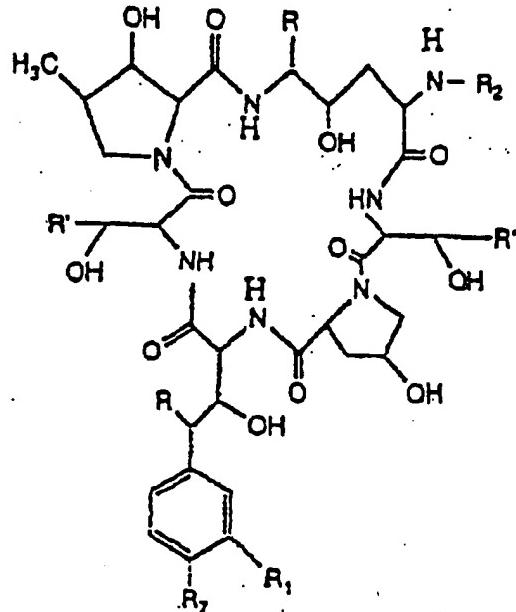
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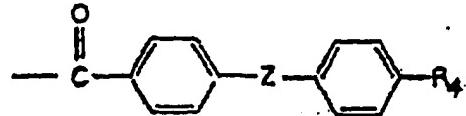
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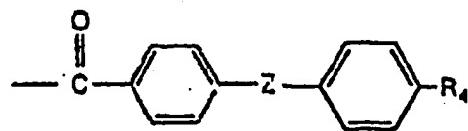
dans laquelle

R' est hydrogène, méthyle, ou $\text{NH}_2\text{C}(\text{O})\text{CH}_2^-$;
 R'' est méthyle ou hydrogène ;
 R est hydroxy ou hydrogène ;
 R₁ est hydroxy, hydrogène ou hydroxysulfonyloxy
 5 R₇ est hydroxy, hydrogène, hydroxysulfonyloxy ou phosphonoxy ;
 R₂ est un groupe acyle représenté par la formule



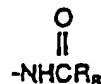
dans laquelle

15 Z est $-\text{C}\equiv\text{C}-$, $-\text{CH}=\text{CH}-$ ou une liaison carbone-carbone ;
 R₄ est un cycloalkyle en C₃ à C₁₂, bicycloalkyle en C₇ à C₁₀, tricycloalkyle en C₇ à C₁₄, phényle, phényle substitué par amino, alkylthio en C₁ à C₁₂, halogène, alkyle en C₁ à C₁₂, alcoxy en C₁ à C₁₂, trifluorométhyle, phényle ou alcoxy en C₁ à C₆ substitué par fluoro, bromo, chloro ou iodo ;
 20 ou R₄ est un groupe cycloalcoxy en C₃ à C₁₂ ;
 ou R₄ est un groupe représenté par la formule $-\text{Y}-\text{R}_6$ dans laquelle Y est $-\text{C}\equiv\text{C}-$ ou $-\text{CH}=\text{CH}-$ et R₆ est un alkyle en C₁ à C₁₂, alkyle en C₁ à C₁₂ substitué par phényle; cycloalkyle en C₃ à C₁₂, phényle, cycloalcényle en C₃ à C₁₂, naphtyle, benzothiazol-2-yle ou phényle substitué par amino, alkylthio en C₁ à C₁₂, halogène, alcényle en C₂ à C₁₂, alcoxy en C₁ à C₁₂, trifluorométhyle, $-\text{O}-(\text{CH}_2)_p-\text{W}-\text{R}_5$ dans laquelle p' est un entier de 2 à 4 ; W est pyrrolidino, pipéridino ou pipérazino, et R₅ est un hydrogène, alkyle en C₁ à C₁₂, cycloalkyle en C₃ à C₁₂, benzyle ou cycloalkylméthyle en C₃ à C₁₂ ; ou alcoxy en C₁ à C₆ substitué par fluoro, bromo, iodo ou chloro ;
 25 ou R₂ est un groupe acyle représenté par la formule

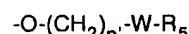


35 dans laquelle Z est $-\text{C}\equiv\text{C}-$ ou $-\text{CH}=\text{CH}-$;

R₄ est un hydrogène ;
 R₄ est un alcoxy en C₁ à C₁₂, alcoxy substitué en C₁ à C₁₂ par cycloalkyle en C₃ à C₁₂, bicycloalkyle en C₇ à C₁₀, tricycloalkyle en C₇ à C₁₄, amino, alkylamino en C₁ à C₄, di-(alkyle en C₁ à C₄)amino, alcanoylamino en C₁ à C₁₂ ou un groupe de formule



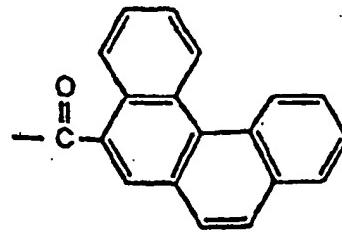
dans laquelle R₈ est un alcoxy en C₁ à C₆ éventuellement substitué par phényle ; ou R₄ est un groupe représenté par la formule



ou

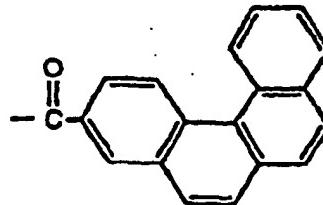
55 R₂ est un groupe choisi parmi

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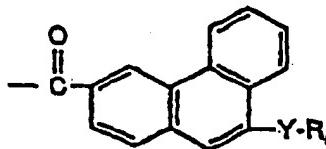
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dans laquelle

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Y et R₆ sont tels que définis ci-dessus ; ouR₂ est un naphtoyle substitué par R₄ dans lequelR₄ est un cycloalkyle en C₃ à C₁₂, bicycloalkyle en C₇ à C₁₀, tricycloalkyle en C₇ à C₁₄, phényle, phényle substitué par amino, alkylthio en C₁ à C₁₂, halogène, alkyle en C₁ à C₁₂, alcoxy en C₁ à C₁₂, trifluorométhyle, phényle ou alcoxy en C₁ à C₆ substitué par fluoro, bromo, chloro ou iodo ;

35

ou R₄ est un groupe représenté par la formule -Y-R₆ dans laquelle Y a les mêmes significations telles que définies ci-dessus et R₆ est un alkyle en C₁ à C₁₂, alkyle en C₁ à C₁₂ substitué par phényle; cycloalkyle en C₃ à C₁₂, phényle, cycloalcényle en C₃ à C₁₂, naphtyle, benzothiazol-2-yle, ou phényle substitué par amino, alkylthio en C₁ à C₁₂, halogène, alkyle en C₁ à C₁₂, alcényle en C₂ à C₁₂, alcoxy en C₁ à C₁₂, trifluorométhyle, -O-(CH₂)_p-W-R₅, ou alcoxy en C₁ à C₆ substitué par fluoro, bromo, iodo ou chloro ;

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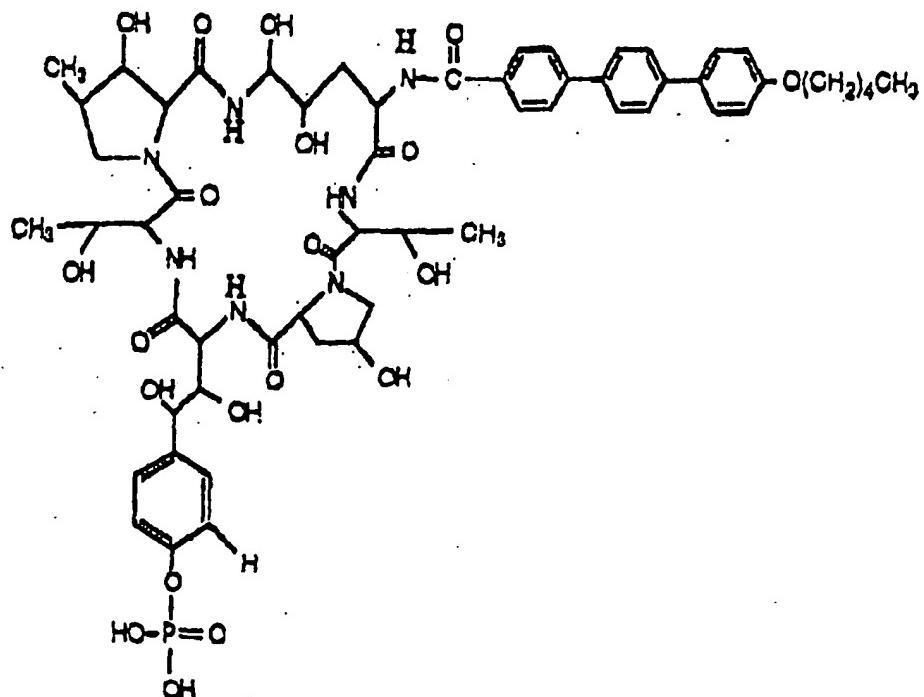
et leurs sels non toxiques pharmaceutiquement acceptables.

45 11. Composé selon la revendication 10 dans lequel R₁ n'est pas un hydroxysulfonyloxy et R₇ n'est ni un hydroxysulfonyloxy ni un phosphonoxy.

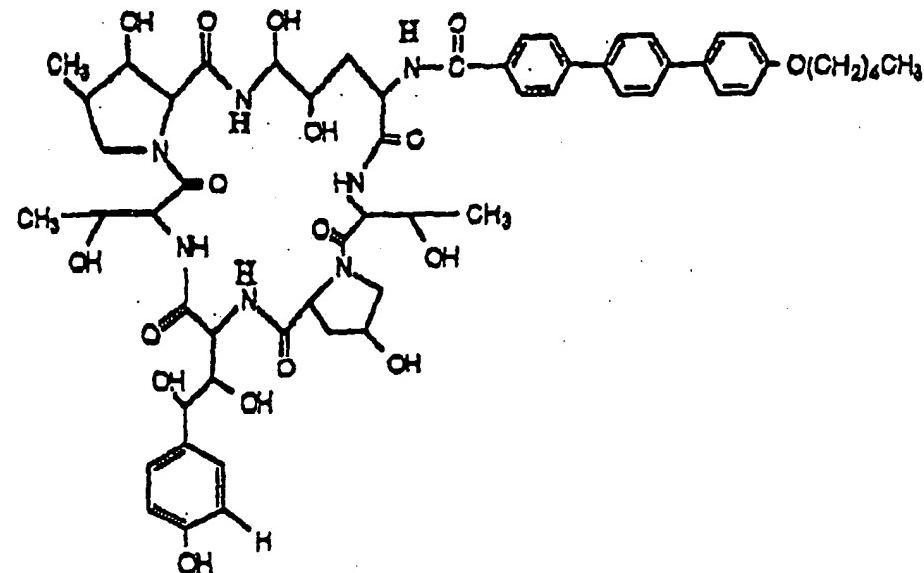
12. Composé de formule

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13. Composé de formule



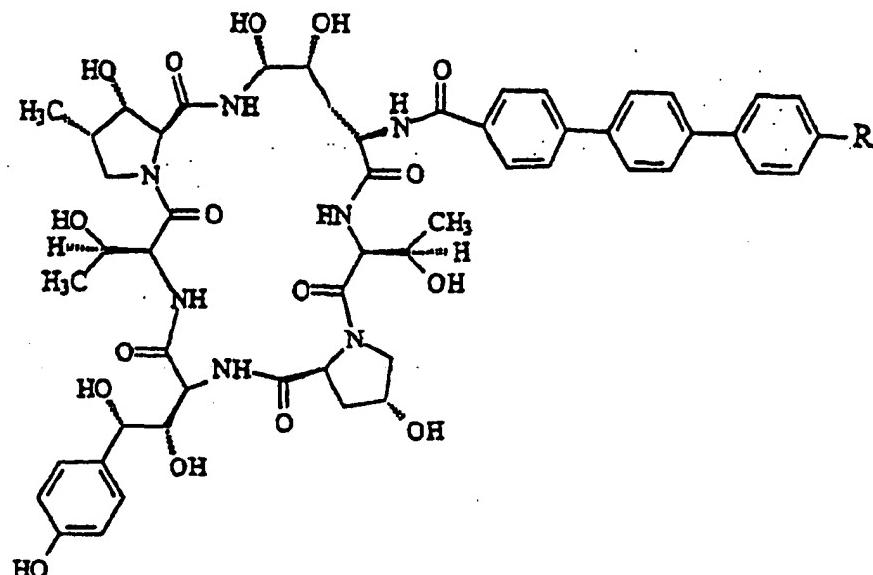
50 14. Composé de formule

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dans laquelle R est -O(CH₂)₃CH₃, -O(CH₂)₄CH₃, -O(CH₂)₅CH₃, -O(CH₂)₂O(CH₂)₃CH₃ ou -O-(CH₂)₂OC(CH₃)₃.

25 15. Composé selon la revendication 14 dans lequel R est -O(CH₂)₄CH₃.

16. Composé selon l'une quelconque des revendications 1-15 à utiliser pour inhiber une activité parasitaire.

17. Composé selon l'une quelconque des revendications 1-15 à utiliser pour inhiber une activité fongique.

30 18. Composé selon l'une quelconque des revendications 1-15 à utiliser pour inhiber la croissance d'organismes responsables d'infections opportunistes chez les individus immunodéprimés.

19. Composé selon l'une quelconque des revendications 1-15 à utiliser pour inhiber la croissance de Pneumocystis carinii.

35 20. Formulation pharmaceutique comprenant un composé selon l'une quelconque des revendications 1-15 et un support pharmaceutique approprié.

40 21. Procédé pour la préparation d'un composé de formule (1) :

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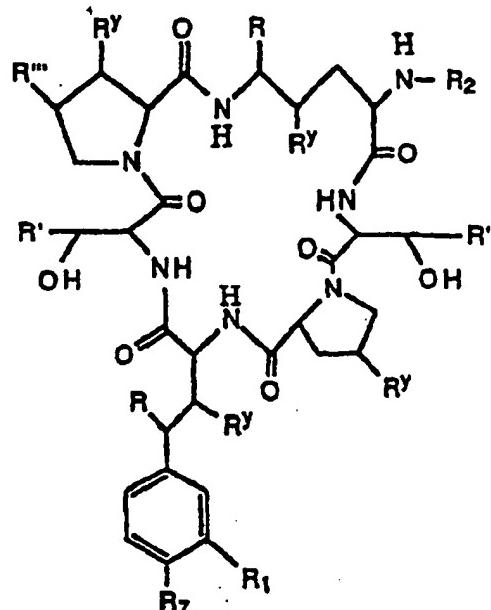
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(1)



dans laquelle

- 25 R' est hydrogène, méthyle, ou $\text{NH}_2\text{C}(\text{O})\text{CH}_2^-$;
 R'' et R''' sont méthyle ou hydrogène ;
 R est hydrogène ;
 R' est hydroxy ou hydrogène ;
 R1 est hydroxy ou hydrogène ;
 30 R7 est hydroxy ou hydrogène ; et
 R2 est hydrogène ou acyle ;

comportant l'étape consistant à exposer un composé de formule (1) dans laquelle R = OH, à un acide fort en présence d'un agent réducteur, dans un solvant approprié.

- 35 22. Procédé de production d'un N-acylhexapeptide cyclique lequel procédé comprend l'acylation d'un noyau amino d'Echinocandin B avec un ester actif d'un acide carboxylique représenté par la formule

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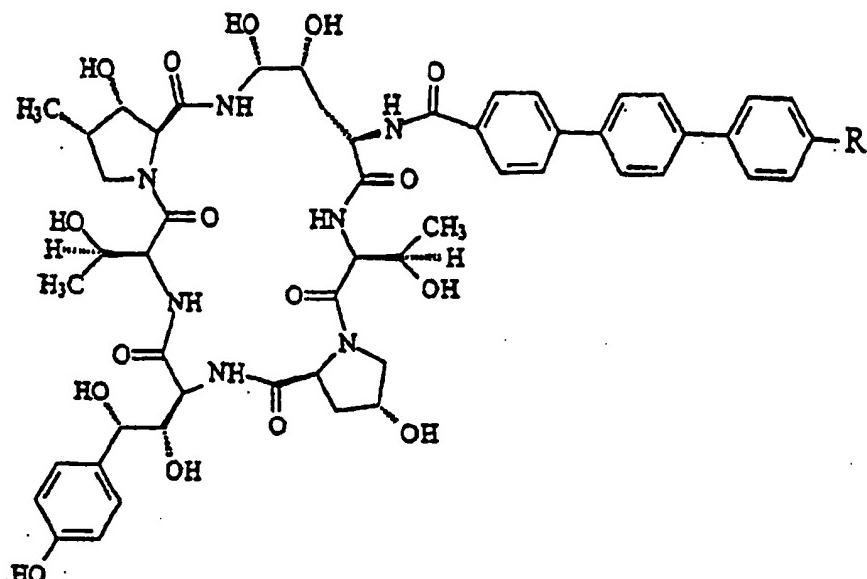
dans laquelle R est $-\text{O}(\text{CH}_2)_3\text{CH}_3$, $-\text{O}(\text{CH}_2)_4\text{CH}_3$, $-\text{O}(\text{CH}_2)_5\text{CH}_3$, $-\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CH}_3$ ou $-\text{O}-(\text{CH}_2)_2\text{OC}(\text{CH}_3)_3$.

45

23. Procédé pour la préparation d'un composé de formule

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5 dans laquelle R est $-O(CH_2)_3CH_3$, $-O(CH_2)_4CH_3$, $-O(CH_2)_5CH_3$, $-O(CH_2)_2O(CH_2)_3CH_3$ ou $-O-(CH_2)_2OC(CH_3)_3$.
 10 lequel procédé comprend l'acylation d'un noyau amino d'Echinocandin B avec un ester actif d'un acide carboxylique
 15 représenté par la formule



- 20
- 25 24. Procédé selon la revendication 22 ou la revendication 23 dans lequel R est $-O(CH_2)_4CH_3$.
- 30 25. Procédé selon l'une quelconque des revendications 22-24 dans lequel l'ester actif est un ester de 2,4,5-trichlorophényle.
- 35 26. Procédé selon l'une quelconque des revendications 22-25 dans lequel le noyau amine d'Echinocandin B est obtenu par N-désacylation d'un hexapeptide cyclique naturel.
- 40 27. Procédé selon la revendication 26 dans lequel l'hexapeptide cyclique naturel est échinocandin B, tétraéchinocandin B, mulundocandin, L-671 329, S 31794/FI, sporiofungin ou FR 901379.

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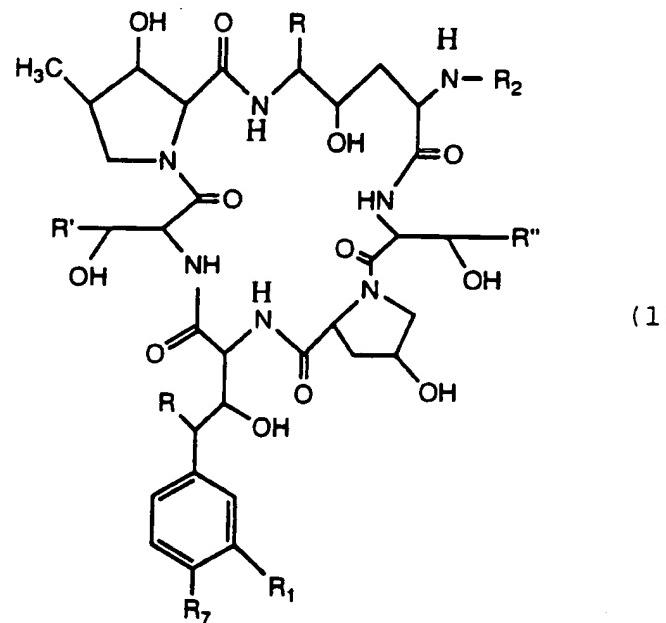
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(54) Cyclic peptide antifungal agents and process for preparation thereof.

(57) Provided are compounds of the formula (1):



wherein R' is hydrogen, methyl or $\text{NH}_2\text{C}(\text{O})\text{CH}_2$;
R'' is methyl or hydrogen;
R is hydroxy or hydrogen;
R₁ is hydroxy, hydrogen, or hydroxysulfonyloxy;
R₇ is hydroxy, hydrogen, hydroxysulfonyloxy or phosphonoxy;
R₂ is a novel acyl side chain. Also provided are novel formulations, methods of inhibiting fungal and parasitic activity, and a process for preparing dihydroxy (R=H) forms of the compounds.

EP 0 561 639 A1

Background of the Invention

This invention relates to cyclic peptide antifungal agents. In particular, it relates to acyl derivatives of the echinocandin class of cyclic peptide antifungal agents; to methods for treating antifungal and parasitic infections, and to formulations useful in the methods.

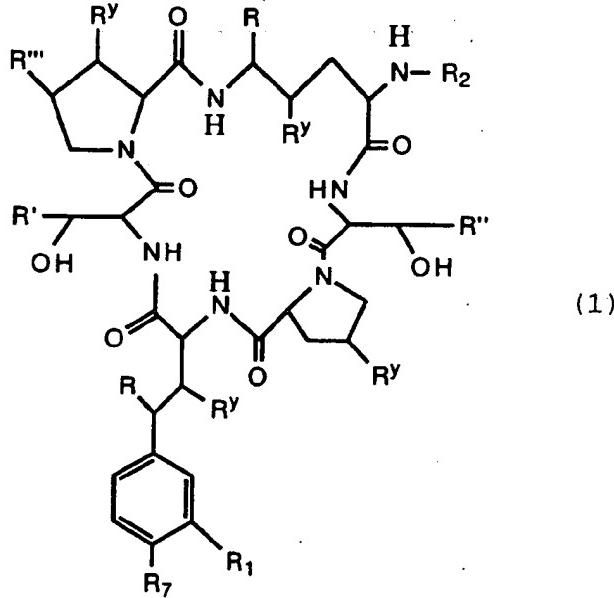
The compounds provided by this invention are semi-synthetic antifungal agents in that they are derived from the cyclic peptide antifungals which are produced by culturing various microorganisms. A number of cyclic peptide antifungals are known. Among these are echinocandin B (A30912A), aculeacin, mulundocandin, sporlofungin, L-671,329, FR901379, and S31794/F1. All such antifungals are structurally characterized by a cyclic hexapeptide core, or nucleus, the amino group of one of the cyclic amino acids bearing a fatty acid acyl group forming a side chain off the core or nucleus. For example, echinocandin B has a linoleoyl side chain while aculeacin has a palmitoyl side chain. These fatty acid side chains of the cyclic hexapeptides can be removed by enzymatic deacylation to provide the free nucleus. (Formula (1), hereinafter, wherein R₂ is hydrogen.) Reacylation of the amino group of the nucleus provides semisynthetic antifungal compounds. For example, the echinocandin B nucleus provides a number of antifungal agents when reacylated with certain unnatural side chain moieties (see *Debono*, U.S. Pat. No. 4,293,489). Among such antifungal compounds is cilofungin which is represented by the formula (1) wherein R is methyl, R₁ is hydrogen and R₂ is p-(n-octyloxy)benzoyl.

Enzymatic deacylation of the cyclic hexapeptides is carried out with deacylase produced by the organism *Actinoplanes utahensis* and related microorganisms as described by Abbott et al., U.S. Pat. No. 4,293,482.

The present invention provides acylated cyclic hexapeptides having unique side chain acyl groups which, inter alia impart enhanced antifungal and antiparasitic potency e.g. against pathogenic strains of Candida albicans. Also provided is a process for removing the aminal and benzylic hydroxy groups to result in a dideoxy compound of formula (1) ($R = H$).

25 Summary of the Invention

The compounds provided by this invention are represented by the following formula (1):



wherein

R' is hydrogen, methyl or $\text{NH}_2\text{C}(\text{O})\text{CH}_2$ -;

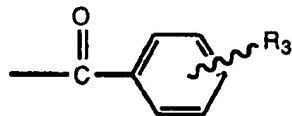
R" and R'" are independently methyl or hydrogen;

R and R^Y are independently hydroxy or hydrogen;

R₁ is hydroxy, hydrogen, or hydroxysulfonyloxy:

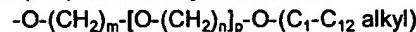
R₂ is hydroxy, hydrogen, hydroxysulfonyloxy or phosphonoxy; and

I) R_2 is a substituted benzoyl group represented by the formula:

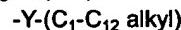


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wherein

A) R₃ is a polyoxa-alkyl group represented by the formula

10 wherein m and n are integers of from 2 to 4, and p is 0 or 1; or

B) R₃ is an unsaturated hydrocarbon group represented by the formula

wherein Y is -C≡C- or -CH=CH-; or

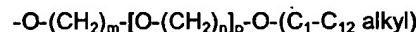
15 C) R₃ is a group of the formula -O-(CH₂)_m-G, wherein m is as defined and G is C₇-C₁₀ bicycloalkyl orC₇-C₁₄ tricycloalkyl; orD) R₃ is quinolyl; orII) R₂ is an acyl group represented by the formula

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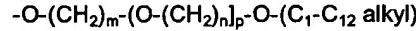


25

wherein

Z is -O-, -C≡C-, -CH=CH-, -CH₂-CH₂-, -CH₂, or a carbon to carbon bond;30 A) R₄ is hydrogen, C₂-C₁₂ alkynyl, C₂-C₁₂ substituted alkynyl, C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, C₁-C₁₂ alkoxy, C₃-C₁₂ cycloalkoxy, naphthyl, pyridyl, thiophenyl, benzothienyl, quinolyl or phenyl; or35 B) R₄ is phenyl substituted by amino, C₁-C₁₂ alkylthio, halogen, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₁-C₁₂ substituted alkyl, C₂-C₁₂ substituted alkenyl, C₂-C₁₂ substituted alkynyl, C₁-C₁₂ alkoxy, trifluoromethyl, phenyl, substituted phenyl, phenyl substituted with a polyoxa-alkyl group represented by the formula

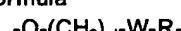
wherein m,n and p are as defined; or

40 C) R₄ is phenyl substituted with C₁-C₆ alkoxy substituted by fluoro, bromo, chloro or iodo; or
D) R₄ is C₁-C₁₂ alkoxy substituted with C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, C₂-C₁₂ alkynyl, amino, C₁-C₄ alkylamino, di-(C₁-C₄ alkyl)amino, C₁-C₁₂ alkanoylamino, phenyl substituted with a polyoxa-alkyl group represented by the formula

wherein m,n and p are as defined; or

45 E) R₄ is C₁-C₁₂ alkoxy substituted with a group of the formula

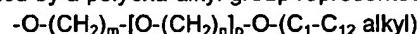
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wherein R₈ is C₁-C₆ alkoxy optionally substituted with phenyl; orF) R₄ is a group represented by the formula55 wherein p' is an integer of from 2 to 4; W is pyrrolidino, piperidino or piperazine, and R₅ is hydrogen, C₁-C₁₂ alkyl, C₃-C₁₂ cycloalkyl, benzyl or C₃-C₁₂ cycloalkylmethyl; orG) R₄ is a group represented by the formula

wherein Y has the same meanings defined above; and

5 R₆ is C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyl; C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, phenyl, C₃-C₁₂ cycloalkenyl, naphthyl, benzothiazolyl, thienyl, indanyl, fluorenyl, phenyl substituted by amino, C₁-C₁₂ alkylthio, halogen, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₁-C₁₂ alkoxy, trifluoromethyl, -O-(CH₂)_p-W-R₅, or C₁-C₆ alkoxy substituted by fluoro, bromo, iodo or chloro; or

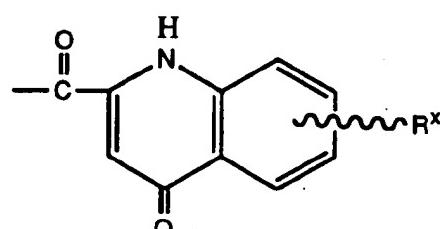
10 R₆ is a phenyl substituted by a polyoxa-alkyl group represented by the formula



15 wherein m,n and p are as defined above; or

III) R₂ is a group having the formula

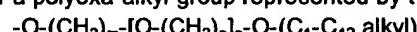
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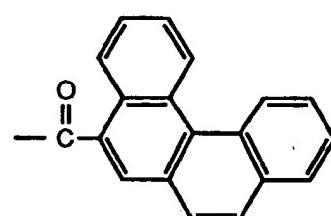
wherein R^x is C₁-C₁₂ alkoxy or a polyoxa-alkyl group represented by the formula



wherein m,n and p are as defined above; or

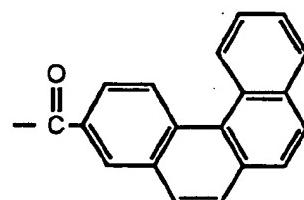
IV) R₂ is a group having the formula

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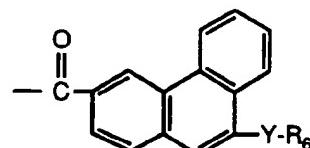
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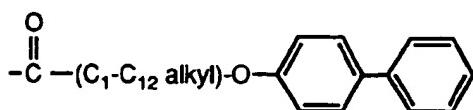
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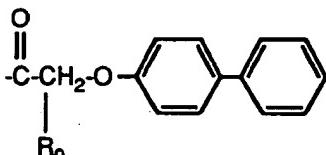
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wherein R_9 is phenyl, C_1-C_{12} alkyl, or C_1-C_{12} alkoxy; or.

V) R_2 is naphthoyl substituted with R_4 , and the pharmaceutically acceptable non-toxic salts thereof; with the proviso that when

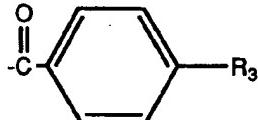
R' is methyl or $\text{NH}_2\text{C}(\text{O})\text{CH}_2-$;
 20 R'' is methyl;
 R''' is methyl;
 R^Y is hydroxy;
 R is hydroxy; and

either a) or b):

- 25 a) R_1 is hydroxysulfonyloxy and R_7 is hydroxy, hydroxysulfonyloxy or phosphonoxy;
 b) R_1 is hydrogen or hydroxysulfonyloxy and R_7 is hydroxysulfonyloxy or phosphonoxy;
 R_2 is not

i)

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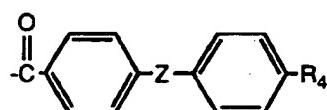
wherein R_3 is

$-\text{O}-(\text{CH}_2)_m-[\text{O}-(\text{CH}_2)_n]_p-\text{O}-(\text{C}_1-\text{C}_{12} \text{ alkyl})$

wherein $p=0$; nor

ii)

40



45

wherein Z is a carbon to carbon bond or $-\text{O}-$ and R_4 is C_1-C_{12} alkoxy; nor

iii) naphthoyl substituted by R_4 wherein R_4 is hydrogen, phenyl, or C_1-C_{12} alkoxy.

Also provided are formulations and methods for inhibiting parasitic and fungal activity which employ the
 50 compounds of the invention, and a process for preparing the dideoxy form of the compounds.

Detailed Description

The term: " C_1-C_{12} alkyl" refers to the straight or branch chain alkyl hydrocarbon groups such as, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl groups; and the like.

The term " C_2-C_{12} alkenyl" refers to groups such as vinyl, 1-propene-2-yl, 1-butene-4-yl, 1-pentene-5-yl, 1-butene-1-yl, and the like.

The term "C₂-C₁₂ alkynyl" refers to such groups as ethynyl, propynyl, pentynyl, butynyl and the like.

The term "C₁-C₁₂ alkylthio" refers to such groups as methylthio, ethylthio, t-butylthio, and the like.

The term "C₁-C₁₂ alkoxy" refers to the straight or branched chain oxyalkyl groups such as, e.g. methoxy, ethoxy, propoxy, butoxy, heptoxy, octyloxy, dodecyloxy, and the like.

5 The term C₃-C₁₂ cycloalkoxy" refers to such groups as cyclopropoxy, cyclobutoxy and the like.

The term "C₃-C₁₂ cycloalkenyl" refers to such groups as cyclopropenyl, cyclobutenyl, cyclopentenyl, and the like.

10 The term "C₁-C₁₂ substituted alkyl," "C₂-C₁₂ substituted alkenyl", and "C₂-C₁₂ substituted alkynyl", denotes the above substituted one or two times with halogen, hydroxy, protected hydroxy, amino, protected amino, C₁-C₇ acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carbamoyloxy, cyano, methylsulfonylamino, phenyl, substituted phenyl, or C₁-C₁₂ alkoxy.

The term "substituted phenyl" is represented by a phenyl group substituted with one, two, or three moieties chosen from halogen, hydroxy, protected hydroxy, cyano, nitro, C₁-C₁₂ alkyl, C₁-C₁₂ alkoxy, carboxy, protected carboxy, carboxymethyl, hydroxymethyl, amino, aminomethyl trifluoromethyl or N-(methylsulfonylamino)

15 The term "C₃-C₁₂ cycloalkyl" refers to such groups as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "C₁-C₄ alkylamino" refers to such groups as methylamino, ethylamino, n-butylamino and the like.

The term "di-(C₁-C₄ alkyl)amino" refers to such groups as dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino, methylethylamino, methyl-n-butylamino, and like tertiary amino groups.

20 The term "C₁-C₁₂ alkanoylamino" refers to such groups as acylamino groups derived from the C₁-C₁₂ carboxylic acids and are exemplified by formamido, acetylamino, propionylamino, butyrylamino, and the like.

The term "C₃-C₁₂ cycloalkylmethyl" refers to those C₃-C₇ cycloalkyls described above further substituted by methyl.

25 The terms "C₇-C₁₀ bicycloalkyl" and "C₇-C₁₄ tricycloalkyl" refer to such groups as bicyclo[2.2.1.]hept-2-yl, bicyclo[2.2.1.]hep-4-en-2-yl, bicyclo[3.3.1.]nona-3-yl, bicyclo[3.3.1.]nona-2-yl, bicyclo[3.2.1.]oct-2-yl, bicyclo[2.2.2.]oct-2-yl, bicyclo[2.2.2.]oct-5-en-2-yl, adamantyl and the like.

The term "dideoxy" refers to compounds of the formula (1) wherein R=H.

The term "inhibiting", such as used in relation to the methods for inhibiting parasitic and fungal activity, is defined to mean its normal definition, i.e., to stop, retard or prophylactically hinder or prevent.

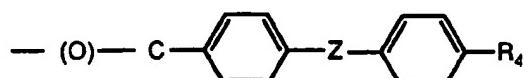
30 The term "activity", as used in relation to parasitic and fungal activity, includes growth thereof and attending characteristics and results from the existence of the parasite or fungus.

The term "contacting", as used in relation to the methods for inhibiting parasitic and fungal activity by contacting a compound of the invention with a parasite or fungus, is defined to mean its normal definition. However, the term does not imply any further limitations to the process, such as by mechanism of inhibition, and the methods are defined to encompass the spirit of the invention, which is to inhibit parasitic and fungal activity by the action of the compounds and their inherent anti-parasitic and anti-fungal properties, or in other words, the compounds, used in the method are the causative agent for such inhibition.

Examples of acyl groups represented by R₂ in formula (1) are benzoyl substituted by polyoxa-alkyl groups such as, e.g., 2-methoxyethoxy (p=0, m=1), 2-ethoxyethoxy, 2-(2-ethoxyethoxy)ethoxy (m=2, p=1, n=2), 3-(2-ethoxyethoxy)-propxy, 3-(2-methoxyethoxy)butoxy, and like groups.

40 Examples of R₃ groups wherein R₂ is benzoyl substituted by an unsaturated hydrocarbon groups -Y-(C₁-C₁₂-alkyl) include e.g., acetylenic groups -C≡C-(C₁-C₁₂ alkyl) and -CH₂=CH₂-(C₁-C₁₂ alkyl) which may be cis- or trans- e.g. propenyl, butenyl, hexenyl, decenyl, and the like; propynyl, butynyl, hexynyl, undecynyl, and like alkynes.

45 Examples of acyl groups wherein R₂ is a group represented by the formula



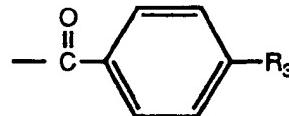
are diphenyl ethers (Z=-O-), diphenyl acetylenes (Z=-C≡C-), stilbenes (Z=-CH=CH-), and biphenyls (Z = a carbon to carbon bond). Among examples of such biphenyl groups, wherein Z is a carbon to carbon bond i.e. a phenyl to phenyl bond, are 4-[4-(butyloxy)phenyl]benzoyl, 4-[4-(cyclobutylmethoxy)-phenyl]benzoyl, 4-[4-cyclopentylmethoxy)phenyl]benzoyl, 4-[4-(cyclohexylethoxy)phenyl]benzoyl, 4-[4-(n-hexyloxy)-phenyl]benzoyl, 4-phenylbenzoyl, 4-[4-(11-aminoundecyloxy)-phenyl]benzoyl, 4-[4-(11-formamidoundecyloxy)phenyl]benzoyl, 4-[4-(isopentylxyloxy)phenyl]benzoyl, and the like. Examples of such diphenyl ether acyl groups R₂ of the formula above wherein Z is an oxygen atom are 4-(4-butyloxyphenoxy)benzoyl, 4-(4-hexyloxyphenoxy)ben-

zoyl, 4-(4-thoxyphenoxy)benzoyl, 4-(4-benzyloxyphenoxy)benzoyl, 4-[4-(3-chlorobutyloxy)phenoxy]benzoyl, 4-(4-dodecyloxyphenoxy)benzoyl, 4-[4-(3-dimethylaminopropoxy)phenoxy]benzoyl and the like. Examples of diphenylacetylene and stilbene acyl groups, R₂, wherein Z is an acetylenic bond or an ethylene bond are 4-styrylbenzoyl, 4-(4-methoxystyryl)benzoyl, 4-(4-butylxystyryl)benzoyl, 4-(phenylethynyl)benzoyl, 4-(4-ethoxyphenylethynyl)benzoyl, 4-(4-cyclohexyloxyphenylethynyl)benzoyl, and the like. Examples of R₂ acyl groups represented by the foregoing formula wherein Z is a carbon to carbon bond and R₄ is represented by the formula -O-(CH₂)_p-W-R₅ are 4-[4-[2-(N-cyclohexylpiperidine-4-yl)ethoxy]phenyl]benzoyl, 4-[4-[2-(N-hexylpiperidine-4-yl)ethoxy]phenyl]benzoyl, 4-[4-[2-(4-benzylpiperidino)ethoxy]phenyl]benzoyl, 4-[4-[2-(4-cyclohexylpiperidino)ethoxy]phenyl]benzoyl and like diphenyl acyl groups. Examples of such acyl groups wherein R₄ is represented by the formula -Y-R₆ include 4-[4-(phenylethynyl)phenyl]benzoyl, 4-[4-(phenylethynyl)phenoxy]benzoyl, 4-[4-(hexynyl)phenyl]benzoyl, 4-[4-(styryl)phenoxy]benzoyl, 4-[4-(4-benzylphenylethynyl)-phenyl]benzoyl, 4-[4-[4-4-methylpiperidino)ethoxy]phenylethynyl]phenyl]benzoyl and like acyl groups. Such acyl groups wherein R₄ is represented by the formula -O-(CH₂)_p-W-R₅ form salts of the basic amino groups of the piperidine and piperazine heterocyclic groups with both organic and inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid and with organic acids such as the sulfonic acids, benzenesulfonic acid, toluenesulfonic acid, methanesulfonic acid, acetic acid, chloroacetic acid, trifluoroacetic acid, benzoic acid, isophthalic acid, salicylic acid, citric acid, malic acid, succinic acid, malonic acid and like acids.

The following tables contain further examples of the cyclic peptides represented by the formula (1). Table 1 contains examples of cyclic peptides wherein the acyl group R₂ is of the formula

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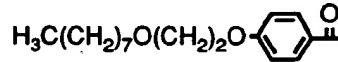
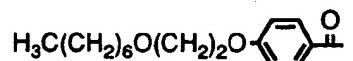
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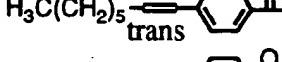
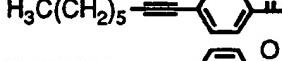
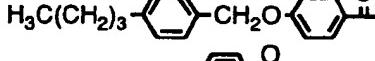
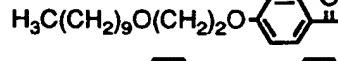
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Table 1R₂

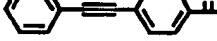
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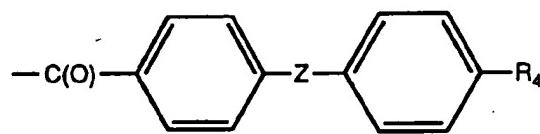


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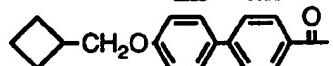
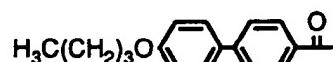
The following Table 2 illustrates the compound of the formula (1) wherein R₂ is represented by the formula

Table 2

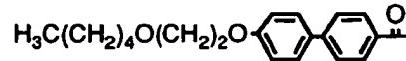
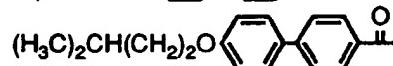
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R₂

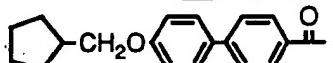
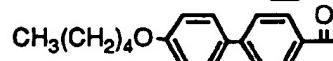
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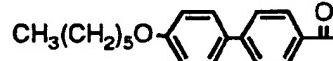
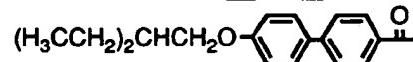
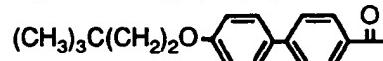
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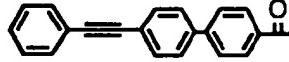
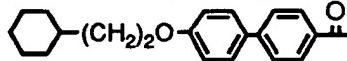
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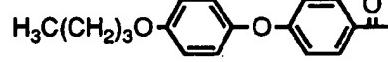
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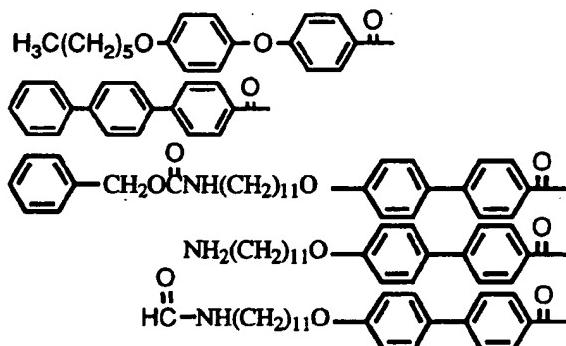
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Table 2 continuedR₂

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20 The following Table 3 illustrates compounds of formula 1 wherein R₂ is of the formula as indicated from
Table 2 and R₄ is represented by the formula -O-(CH₂)_p-W-R₅.

Table 3

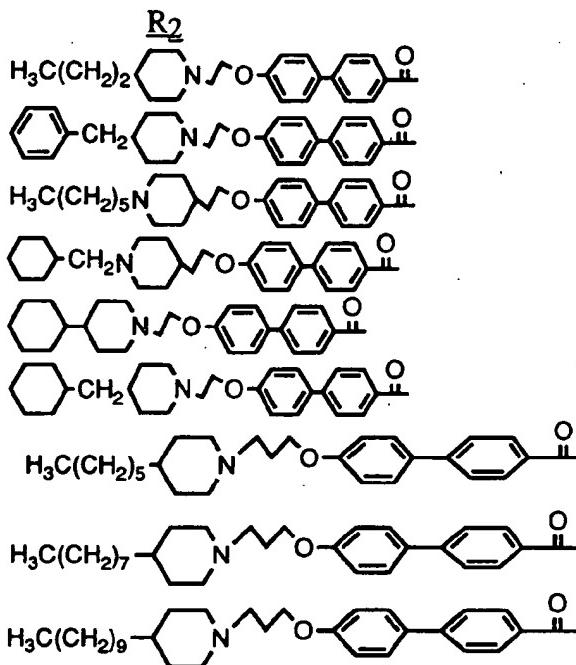
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50 The acyl cyclohexapeptides represented by formula (1) exhibit antiparasitic activity, for example, they are especially active against the infectious fungi Candida albicans and Candida parapsilosis. They also exhibit significant activity against Aspergillus fumigatus. They are active both in vitro and in vivo and accordingly are useful in combating systemic fungal infections.

55 The compounds of the invention also inhibit the growth of certain organisms primarily responsible for opportunistic infections in immunosuppressed individuals. For example the compounds of the invention inhibit the growth of Pneumocystis carinii the causative organism of pneumocystis pneumonia in AIDS sufferers.

The antifungal activity of the compounds of the invention is determined in vitro in standard agar dilution tests and disc-diffusion tests wherein minimum inhibitory concentrations of the test compounds obtained. Stan-

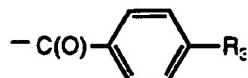
dard in vivo tests in mice are used to determine the effective dose of the test compounds in controlling systemic fungal infections.

Tables 4A-E below contain the minimum inhibitory concentrations (MIC) in micrograms per milliliter (mcg/ml) for compounds of the invention against Candida albicans and Candida parapsilosis, and for certain compounds, the effective dose, ED₅₀, in mice.

In Tables 4A-E, R'=CH₃, R''=CH₃, R'''=OH, R₇=OH and R₁=H, In Tables 4A-D, R=OH, while in Table E, R=H.

In the Table 4A, R₂ is of the formula

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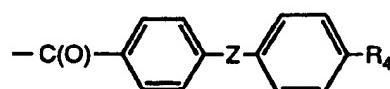


with R₃ being as indicated in the Table 4.

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In Table 4B, R₂ is of the formula

20



where Z is -O- and R₄ is as indicated.

Table 4C is as Table 4B, except Z is a carbon-carbon bond.

Table 4D indicates compound activities in which R₂ is as defined.

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In Table 4E, dideoxy (where R=H) compounds are illustrated with R₂ as indicated.

TABLE 4A

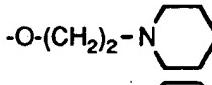
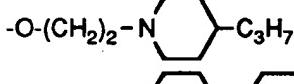
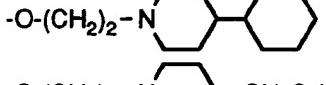
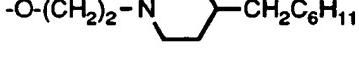
	R ₃	MIC (mcg/ml)		ED ₅₀ (mg/kg)
		C.alb.	C.parap.	
	-O(CH ₂) ₂ -O-(CH ₂) ₂ -O-C ₂ H ₅	>20	40	-
	-O-(CH ₂) ₂ -O-C ₅ H ₁₁	>20	40	-
35	-O-(CH ₂) ₂ -OC ₇ H ₁₅	10	40	30.3
	-O-(CH ₂) ₂ -O-C ₈ H ₁₇	2.5	80	4.4
	-O-(CH ₂) ₂ -O-C ₁₀ H ₂₁	0.625	5	9.5
40	-C≡C-C ₅ H ₁₁	2.5	29	10.5
	-CH=CH-C ₆ H ₁₃ (trans)	0.312	20	4.4
	-C≡C-C ₈ H ₁₇	0.156	10	-

45

TABLE 4B

	MIC (mcg/ml)		ED ₅₀ (mg/kg)	
	R ₄	C.alb.		
	-O-C ₄ H ₉	>20	40	-
55	-O-C ₆ H ₁₃	1.25	>20	22.9

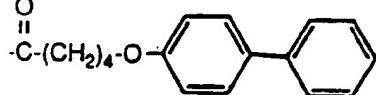
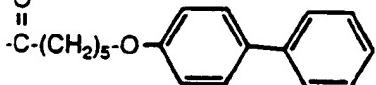
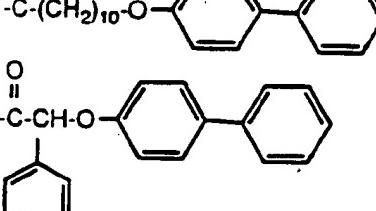
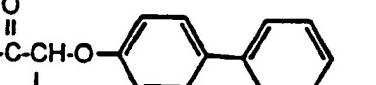
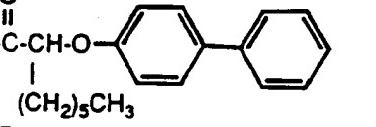
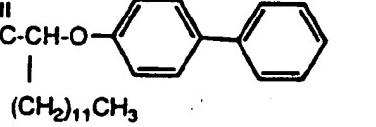
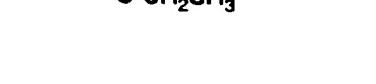
TABLE 4C

5	R ₄	MIC (mcg/ml)		ED ₅₀ (mg/ml)
		C.alb.	C.parap.	
	-O-C ₄ H ₉	0.78	10	0.84
10	-O-CH ₂ -cyclobutyl	0.312	10	2.50
	-O-CH ₂ -cyclopentyl	0.039	2.5	1.20
	-O-C ₅ H ₁₁	0.156	0.625	1.86
15	-O-C ₆ H ₁₃	0.039	1.25	1.10
	-O-CH ₂ CH ₂ -cyclohexyl	0.039	20	1.6
	-O-CH ₂ -CH(C ₂ H ₅)-C ₂ H ₅	0.039	2.5	4.6
	-O-CH ₂ -CH ₂ -CH(CH ₃) ₂	0.309	5	2.00
20	-O-CH ₂ -CH ₂ -C(CH ₃) ₃	0.039	2.5	2.21
	-O-(CH ₂) ₂ -O-C ₅ H ₁₁	1.25	20	0.60
	-C≡C-C ₄ H ₉	0.039	2.5	1.20
25	-C≡C-C ₆ H ₅	0.039	0.625	0.60
	-C ₆ H ₅	0.078	10	1.3
	-O-(CH ₂) ₂ -N(CH ₃) ₂	>20	>20	-
30	-O-(CH ₂) ₂ -N 	>20	>20	-
	-O-(CH ₂) ₂ -N 	5	>20	3.0
35	-O-(CH ₂) ₂ -N 	0.312	40	0.64
	-O-(CH ₂) ₂ -N 	0.039	5	0.24
40				
45				

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TABLE 4D

5	Σ_2	MIC (mcg/ml)	
		<i>C. alb.</i>	<i>C. parap.</i>
10		40	>80
15		1.25	80
20		0.0039	2.5
25		5	>80
30		80	>80
35		80	>80
40		10	>80
45		>80	>80

50

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TABLE 4D continued

	<u>R₂</u>	MIC (mcg/ml)	
		<u>C. alb.</u>	<u>C. parap.</u>
10			
15		20	>80
20		10	>80
25		20	>80
30		20	>80
35		0.039	5
40		0.078	0.312

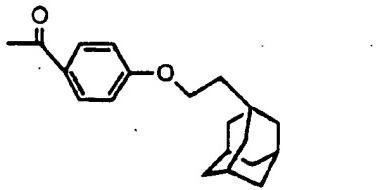
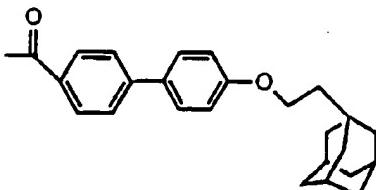
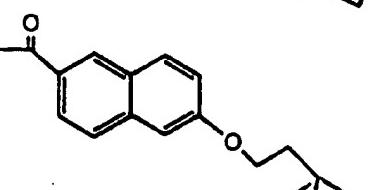
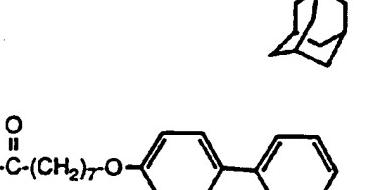
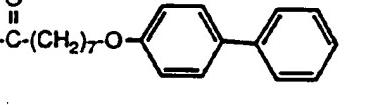
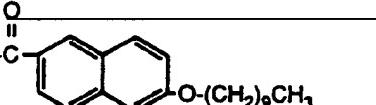
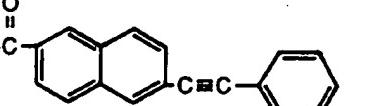
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TABLE 4D continued

	32	MIC (mcg/ml)	
		C.alb.	C.parap.
10			
15		0.5	80
20		0.005	0.156
25			
30		0.039	0.156
35		0.156	20
40		0.005	0.312
45		0.312	5
50			

55

TABLE 4D continued

	β_2	MIC (mcg/ml)	C.alb.	C. parap.
5				
10		0.312		>80
15		0.078		>20
20				
25				
30				
35				
40				
45				
50				
55				

TABLE 4E

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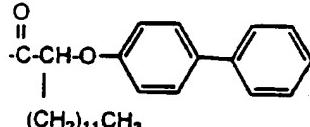
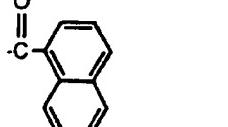
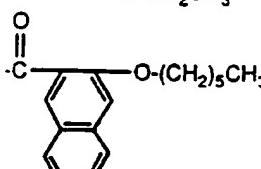
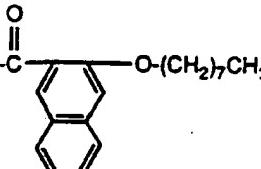
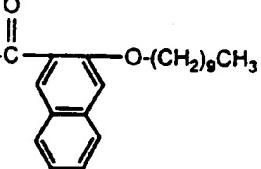
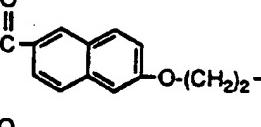
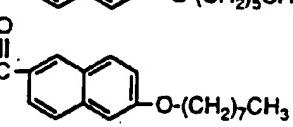
	R ₂	MIC (mcg/ml)	C. alb.	C. parap.
10		0.039	5.0	
15		>20	1.25	
20		0.039	2.5	
25		>80	>80	
30		1.25	40	
35		0.005	2.5	
40		0.0098	0.625	
45		80	>80	
		20	>80	
		40	>80	

50

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TABLE 4E continued

5

	β_2	MIC (mcg/ml)	C. alb.	C. parap.
10			1.25	>80
15			>80	>80
20				
25		10	>80	
30		10	>80	
35		5.0	>80	
40		1.25	>80	
45		0.078	1.25	
		0.039	0.125	

50

55

TABLE 4E continued

	<u>R₂</u>	MIC (mcg/ml)	
		C.alb.	C.parap.
5			
10		0.156	0.625
15		0.156	5.0
20		0.625	80
25			
30		0.005	0.156
35		0.039	0.156
40			

The non-dideoxy compounds of the invention (formula (1) are prepared with the amino nuclei of the cyclic hexapeptides which are represented by the formula when R₂ is hydrogen. These amino nuclei are obtained from the known natural products by the known enzymatic deacylation by which the fatty acid side chains of the natural compounds are removed. For example, echinocandin B which can be represented by the formula (1) wherein R'=R''=R'''= methyl, R is OH, RY is hydroxy, R₁ is H, R₇ is OH, and R₂ is linoleoyl, is deacylated to provide the echinocandin B nucleus (R₂=H) with the deacylase produced by the organism Actinoplanes utahensis as described by U.S. Patent Nos. 4,293,482 and 4,304,716.

The known natural cyclic hexapeptides which are N-deacylated to provide the amino nuclei starting materials include echinocandin B (also known as A-30912A), aculeacin (palmitoyl side chain), tetrahydooechinocandin B (stearoyl side chain), mulundocandin (branched C₁₅ side chain), L-671,329 (C₁₆ branched side chain), S 31794/F1 (tetradecanoyl side chain), sporiofungin (C₁₅ branched side chain) and FR901379 (palmitoyl side chain). The amino nuclei obtained by the N-deacylation are then acylated by employing known amino acylation procedures to provide the N-acyl cyclic hexapeptides represented by the formula (1) wherein R₂ represents the acyl groups defined hereinabove. The acylating moiety is preferably an active ester of the carboxylic acid RCOOH such as the 2,4,5-trichlorophenyl ester. The R₂COOH precursor acids are prepared by the hydrolysis of the nitrile R₂CN or the ester R₂COOC₁-C₄ alk. These nitrile and ester intermediates are prepared by known

methods.

The alkoxy aromatic (ie. phenyl and biphenyl) compounds of Tables 5-10 are prepared by one of the two following procedures:

5 A. The hydroxyaromatic compound (1 equivalent) is dissolved in acetonitrile (200-300 ml) and a base, such as potassium t-butoxide or potassium carbonate, (1-equivalent), is added. An alkyl bromide, iodide, or p-toluenesulfonate (1 equivalent) is then added and the solution is refluxed for 6 hours. The solvent is evaporated in vacuo and the residue is dissolved in ether and 2N sodium hydroxide. The ether layer is dried over magnesium sulfate and evaporated to give the alkoxyaromatic product.

10 B. The hydroxyaromatic compound (1 equivalent), alkyl alcohol (1 equivalent), and triphenylphosphine (1 equivalent) are dissolved in tetrahydrofuran (200-300 ml) and diethylazodicarboxylate (1 equivalent) is added dropwise over 10 minutes at room temperature. After 17 hours the solvent is removed in vacuo and the residue is dissolved in ether. This organic layer is extracted with 2N sodium hydroxide solution, dried over magnesium sulfate, and evaporated to give a product which is crystallized from ether/pentane or, if the product contains a tertiary amine, the hydrochloride salt is formed and crystallized from methanol/ethyl acetate.

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TABLE 5

Alkyl halide or tosylate	Wt. g	Method	R ₁	R ₂	Wt. g
I(CH ₂) ₃ CH ₃	9.4	A	-(CH ₂) ₃ CH ₃	CN	3.2
CH ₃  SO ₃ -CH ₂ 	12.3	A	CH ₂ 	CN	5.3
Br(CH ₂) ₂ CH(CH ₃) ₂	7.7	A	-(CH ₂) ₂ CH(CH ₃) ₂	CN	9.2
CH ₃  SO ₃ -(CH ₂) ₂ O(CH ₂) ₄ CH ₃	7.6	A	(CH ₂) ₂ O(CH ₂) ₄ CH ₃	CN	4.8
Br(CH ₂) ₄ CH ₃	15.3	A	-(CH ₂) ₄ CH ₃	CN	20.3
CH ₃  SO ₃ -CH ₂ 	13.0	A	CH ₂ 	CN	12.2
CH ₃  SO ₃ -(CH ₂) ₂ C(CH ₃) ₃	13.1	A	(CH ₂) ₂ C(CH ₃) ₃	CN	11.8
BrCH ₂ CH(CH ₂ CH ₃) ₂	8.5	A	-CH ₂ CH(CH ₂ CH ₃) ₂	CN	3.0
I(CH ₂) ₅ CH ₃	10.8	A	-(CH ₂) ₅ CH ₃	CN	11.4
Br(CH ₂) ₂ 	4.2	A	(CH ₂) ₂ 	CO ₂ CH ₃	4.5

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TABLE 6

Alcohol	wt. g	Method	R	wt. g
<chem>O=Cc1ccc(cc1)OCCN2CC(O)CC(C)c3ccccc3C2</chem>	3.6	B	<chem>O=Cc1ccc(cc1)OCCN2CC(C)c3ccccc3C2</chem>	6.2
<chem>O=Cc1ccc(cc1)OCCN2CC(C)c3ccccc3C2</chem>	6.1	B	<chem>O=Cc1ccc(cc1)OCCN2CC(C)c3ccccc3C2</chem>	4.3
<chem>O=Cc1ccc(cc1)OCCN2CC(C)c3ccccc3C2</chem>	0.5	B	<chem>O=Cc1ccc(cc1)OCCN2CC(C)c3ccccc3C2</chem>	0.8
<chem>O=Cc1ccc(cc1)OCCN2CC(C)c3ccccc3C2</chem>	0.5	B	<chem>O=Cc1ccc(cc1)OCCN2CC(C)c3ccccc3C2</chem>	0.5
<chem>O=Cc1ccc(cc1)OCCN2CC(C)c3ccccc3C2</chem>	2.3	B	<chem>O=Cc1ccc(cc1)OCCN2CC(C)c3ccccc3C2</chem>	1.3
<chem>O=Cc1ccc(cc1)OCCN2CC(C)c3ccccc3C2</chem>	9.3	B	<chem>O=Cc1ccc(cc1)OCCN2CC(C)c3ccccc3C2</chem>	9.6

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TABLE 7

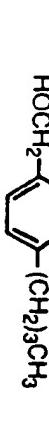
<u>Tosylate or alcohol</u>	<u>wt.</u>	<u>Method</u>		<u>wt.</u>
	23.4	A		20.9
	25.8	A		7.9
	27.1	A		21.0
	10.0	B		13.6

TABLE 8

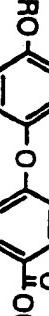
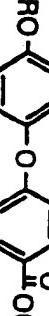
<u>Alkyl halide</u>	<u>wt.</u>	<u>Method</u>		<u>wt.</u>
$(CH_2)_3CH_3$	6.1	A		12.3
$(CH_2)_5CH_3$	4.3	A		4.7

Table 9

<u>Alkylhalide or tosylate</u>	<u>Wt.</u>	<u>Method</u>	<u>R</u>	<u>Wt.</u>
$\text{I}(\text{CH}_2)_2\text{ClH}_3$	2.6	A	$-(\text{CH}_2)_2\text{CH}_3$	4.4
H_3C $\text{SO}_3 \cdot (\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CH}_3$	2.7	A	$-(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CH}_3$	2.6
H_3C $\text{SO}_3 \cdot (\text{CH}_2)_2\text{OC}(\text{CH}_3)_3$	2.7	A	$-(\text{CH}_2)_2\text{OC}(\text{CH}_3)_3$	2.6

Table 10

<u>Alkylhalide or tosylate</u>	<u>Wt.</u>	<u>Method</u>	<u>R</u>	<u>Wt.</u>
$\text{I}(\text{CH}_2)_2\text{ClH}_3$	3.8	A	$-(\text{CH}_2)_2\text{CH}_3$	1.4
H_3C $\text{SO}_3 \cdot (\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CH}_3$	3.6	A	$-(\text{CH}_2)_2\text{O}(\text{CH}_2)_3\text{CH}_3$	5.1
H_3C $\text{SO}_3 \cdot (\text{CH}_2)_2\text{OC}(\text{CH}_3)_3$	4.9	A	$-(\text{CH}_2)_2\text{OC}(\text{CH}_3)_3$	5.2

TABLE II

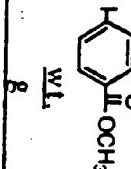
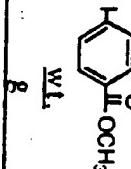
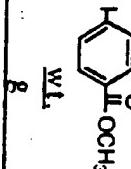
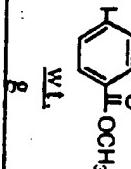
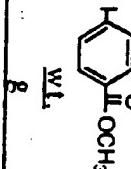
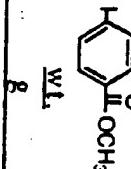
Acetylene or olefin	wt. g		wt. g	R	wt. g
H≡-(CH ₂) ₅ CH ₃	12.1		28.8	-C≡-(CH ₂) ₅ CH ₃	26.2
H≡-(CH ₂) ₅ CH ₃	6.1		14.4	-CH≡-(CH ₂) ₅ CH ₃ (trans)	0.6
H≡-(CH ₂) ₇ CH ₃	15.2		28.8	-C≡-(CH ₂) ₇ CH ₃	28.1
H≡-C ₆ H ₅	1.9		5.1	-C≡-C ₆ H ₅	1.9
H≡-Si(CH ₃) ₃	4.3		11.5	-≡-Si(CH ₃) ₃	11.2

TABLE 12

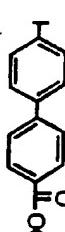
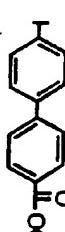
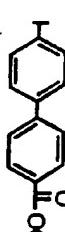
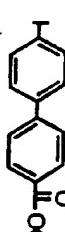
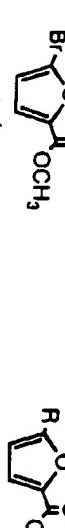
Acetylene	wt. g		wt. g	R	wt. g
H≡-C ₆ H ₅	1.8		6.0		2.6
H≡-(CH ₂) ₃ CH ₃	1.4		6.0		5.1
H≡-Si(CH ₃) ₃	10.9		40.0		23.3

TABLE 13

Acetylene	wt. g		wt. g	R	wt. g
H≡-(CH ₂) ₇ CH ₃	7.6		11.3		11.4

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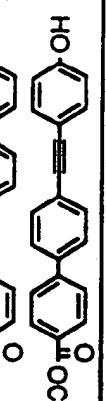
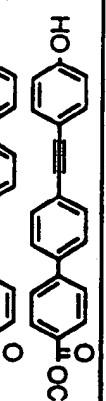
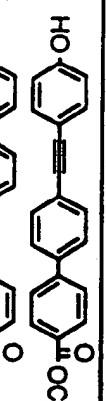
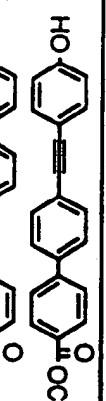
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TABLE 14

Acetylene	wt.	Halide	wt.	Product	wt.
	10.5		9.7		10.2
	22.2		34.4		19.4
	1.2		1.2		1.5
					

The aromatic boronic acids listed in Table 15 were prepared by the following procedure:

An aromatic halid (1 equivalent) is cooled to -78°C in tetrahydrofuran solvent. Butyl lithium (1.2 equivalents) is added. After 15 min triisopropyl borate (2 equivalents) is added and after 10 min of stirring the cooling bath is removed. When the reaction has warmed to room temperature water is added to quench the reaction followed by 1N HCl. The organic layer is removed under reduced pressure leaving a solid precipitate which is collected by filtration. This solid is washed with hexane leaving the pure boronic acid.

The terphenyl esters listed in Table 16 were made in the following manner:

An aromatic boronic acid (1 equivalent), methyl 4-iodobenzoate (1 equivalent), and potassium carbonate (1.5 equivalents) were mixed in a nitrogen-purged toluene solution. Alternatively, the trichloro phenyl ester of iodobenzoate may be used. Added tetrakis(triphenylphosphine)palladium (0.03 equivalents) and refluxed for 7 hrs. The solution was decanted to remove the potassium carbonate and reduced in vacuo. The residue was triturated with acetonitrile and the product solid was collected by filtration.

TABLE 15

R=Br	Wt. (g)	R=B(OEt) ₂	Wt. (g)
	10.6		6.1
	31.0		12.0
	5.0		4.1
			5.7

TABLE 16

R	(HO) ₂ B-	Wt. (g)	H ₃ COOC-	Wt. (g)	H ₃ COOC-	Wt. (g)
-O(CH ₂) ₃ CH ₃	5.0	3.2			4.2	
-O(CH ₂) ₄ CH ₃	6.0	3.7			5.2	
-O(CH ₂) ₅ CH ₃	3.4	2.8			3.5	
-O(CH ₂) ₂ O(CH ₂) ₃ CH ₃	3.7	3.6			3.7	
-O(CH ₂) ₂ OC(CH ₃) ₃	1.8	1.5			2.2	

The aromatic nitriles or carboxylate esters described in Tables 5-16 can be converted to carboxylic acids

by one of the two following hydrolysis procedures:

A. An aromatic nitrile is dissolved in ethanol and an excess of 50% sodium hydroxide solution and refluxed for 2 hours. Water is added until a solid precipitate forms. The precipitate is collected by filtration, added to dioxane and 6N hydrochloric acid solution and refluxed for 17 hours. Water is added and the carboxylic acid product crystallizes and is collected by filtration and dried under vacuum.

B. A carboxylate methyl ester is dissolved in methanol, excess 2N sodium hydroxide solution is added and the solution is refluxed for 5 hours. The solution is made acidic with excess hydrochloric acid and water is added until a precipitate forms. The carboxylic acid is collected by filtration and dried under vacuum.

The carboxylic acids are converted to 2,4,5-trichlorophenyl esters shown in Tables 17-25 by the following

10 general procedure:

The aromatic acid (1 equivalent), 2,4,5-trichlorophenol (1 equivalent), and N,N'-dicyclohexylcarbodiimide (1 equivalent) are dissolved in methylene chloride. The mixture is stirred for 17 hours after which it is filtered. The filtrate is evaporated to dryness and the residue is dissolved in ether, filtered, and pentane is added until crystallization begins. The crystalline product is collected by filtration and dried under vacuum.

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TABLE I7

R		2,4,5-trichlorophenol ester	
	wt. g	wt. g	
- $(CH_2)_3CH_3$	1.9	1.8	
- $CH_2-\text{Cyclobutyl}$	4.2	4.4	
- $(CH_2)_2CH(CH_3)_2$	3.0	1.7	
- $(CH_2)_2O(CH_2)_4CH_3$	2.2	1.3	
- $(CH_2)_4CH_3$	5.7	5.1	
- $CH_2-\text{Cyclopentyl}$	4.4	3.1	
- $(CH_2)_2C(CH_3)_3$	2.3	2.6	
- $CH_2CH(CH_2CH_3)_2$	1.5	0.8	
- $(CH_2)_5CH_3$	5.3	4.8	
- $(CH_2)_2-\text{Cyclohexyl}$	3.1	1.0	
- $(CH_2)_2-N-\text{Cyclohexyl}-\text{CH}_2-$ CH_2-CH_3	3.3	1.5	
- $(CH_2)_2-N-\text{Cyclohexyl}-\text{CH}_2-$ $\text{CH}_2-\text{C}_6H_5$	3.0	2.3	
- $(CH_2)_2-\text{Cyclohexyl}-\text{CH}_2-$ $N-(CH_2)_5CH_3$	1.0	1.0	
- $(CH_2)_2-\text{Cyclohexyl}-\text{CH}_2-$ $N-\text{CH}_2-\text{C}_6H_5$	2.0	0.8	
- $(CH_2)_2-N-\text{Cyclohexyl}-\text{CH}_2-$ C_6H_5	7.2	0.8	
- $(CH_2)_2-N-\text{Cyclohexyl}-\text{CH}_2-$ C_6H_5	7.5	7.3	

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TABLE 18

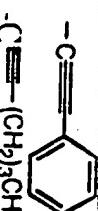
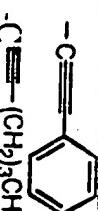
<u>R</u>	<u>2,4,5-trichlorophenol ester</u>
	<u>wt.</u>
	<u>g</u>
	2.0
	0.6
	1.1
	0.6

TABLE 19

<u>R</u>	<u>2,4,5-trichlorophenol ester</u>
	<u>wt.</u>
	<u>g</u>
	5.6
	7.8
	6.4
	4.0
	3.2

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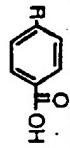
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TABLE 20

	wt.	wt.
R	g	g
-C≡-(CH ₂) ₅ CH ₃	4.6	3.5
-CH=-(CH ₂) ₅ CH ₃ (trans)	1.2	0.5
-C≡-(CH ₂)CH ₃	11.1	13.2
-C≡-C(=O)cyclohexyl	1.5	1.5

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TABLE 21

	wt.	2,4,5-trichlorophenol ester	wt.
R	g		g
-C(CH ₂) ₃ Cl ₃	5.8		1.4
-C(CH ₂) ₅ Cl ₃	3.8		2.4

TABLE 22

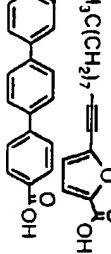
Carboxylic acid	wt.	2,4,5-trichlorophenol ester	wt.
	g		g
	8.3		13.2
	11.8		1.2

TABLE 23

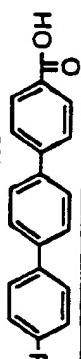
R		2,4,5-Trichlorophenol ester Wt. (g)
-O(CH ₂) ₃ CH ₃	3.3	4.8
-O(CH ₂) ₄ CH ₃	3.0	2.5
-O(CH ₂) ₅ CH ₃	2.3	3.9
-O(CH ₂) ₂ O(CH ₂) ₃ CH ₃	3.3	4.4
-O(CH ₂) ₂ OC(CH ₃) ₃	1.3	1.9

TABLE 24

R		2,4,5-Trichlorophenol ester Wt. (g)
-O(CH ₂) ₃ CH ₃	6.5	5.2
-O(CH ₂) ₂ O(CH ₂) ₃ CH ₃	4.9	5.2
-O(CH ₂) ₂ OC(CH ₃) ₃	4.6	2.1

TABLE 25

R		2,4,5-Trichlorophenol ester Wt. (g)
-O(CH ₂) ₃ CH ₃	2.9	2.5
-O(CH ₂) ₂ O(CH ₂) ₃ CH ₃	2.0	1.5
-O(CH ₂) ₂ OC(CH ₃) ₃	2.0	1.3

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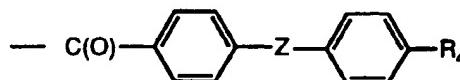
The dideoxy compounds of formula (1) are prepared by removing the benzylic and aminal hydroxy groups. The process includes subjecting a non-dideoxy compound of formula (1) (wherein R₂ may be hydrogen or acyl) to a strong acid such as trichloroacetic acid, trifluoroacetic acid or borontrifluoride etherate with trifluoroacetic acid being preferred, and a reducing agent, such as sodium cyanoborohydride or triethylsilane, with triethylsilane being preferred. The reaction takes place at temperatures between -5 and 70°C, and in a suitable solvent such as methylene chloride, chloroform or acetic acid, with dichloromethane being preferred. The acid should be present in an amount of 2 to 60 moles per mole of substrate, and the reducing agent should be present in an amount of 2 to 60 moles per mole of substrate. This process affords selective removal of the aminal and

benzylic hydroxy groups.

The compounds represented by the formula (1) have improved properties over the previously known N-acyl hexapeptide antifungals. For example, in general these compounds exhibit oral bioavailability, a property which is important for any systemic antifungal agent. Also, numerous N-acyl compounds of the formula (1) have enhanced antifungal activity and enhanced water solubility.

Among the N-acyl hexapeptides represented by the formula (1) certain are preferred embodiments of the invention. The compounds wherein R₂ is a diphenyl acyl group

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wherein Z is a carbon to carbon bond and R₄ is an alkoxy, cycloalkoxy or cycloalkylalkoxy group are preferred antifungals. Also preferred compounds are represented when Z is a carbon to carbon bond and R₄ is -Y-R₆ and R₆ is C₁-C₁₂ alkyl phenyl or substituted phenyl and Y is an acetylenic bond.

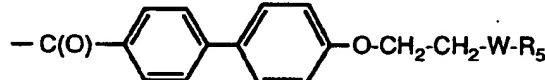
A further preferred group of N-acyl hexapeptides is represented when Z is a carbon to carbon bond and R₄ is represented by -O-(CH₂)_p-W-R₅ and wherein W is a piperidine group.

Examples of preferred compounds of the above first mentioned group include 4-(4-alkoxyphenyl)benzoyl wherein the alkoxy group is preferably a C₅-C₁₀ alkoxy group or C₁-C₄ alkoxy substituted by C₃-C₇ alkyl. Examples of such preferred compounds are represented by the formula 1 wherein R₂ is 4-(4-n-hexyloxyphenyl)benzoyl, 4-(4-n-heptyloxyphenyl)benzoyl, 4-(4-n-octyloxyphenyl)benzoyl, 4-[4-(3,3-dimethylbutoxy)phenyl]benzoyl, 4-[4-(2-cyclopentyl-ethoxy)phenyl]benzoyl and 4-[4-(2-cyclohexyloxyethoxy)phenyl]benzoyl.

Examples of the second above mentioned preferred compounds wherein R₄ is -Y-R₆ include 4-[4-(phenylethyynyl)phenyl]benzoyl and 4-[4-(n-butylethyynyl)phenyl]benzoyl.

Examples of preferred compounds of the invention wherein R₄ represents -O-(CH₂)_p-W-R₅ are represented when R₂ has the formula

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wherein W-R₅ is piperidino, 4-n-propylpiperidino, 4-benzylpiperidino, 4-cyclohexylpiperidino, 4-cyclohexylmethylpiperidino, and the pharmaceutically acceptable acid addition salts such as the hydrochloride salts, the sulfate salts or the phosphate salts.

Preferred cyclohexylpeptide compounds are represented by the formula 1 wherein R'=R''=methyl, R₁ is hydrogen and R₂ is a preferred acyl group as defined hereinabove.

Table 26 is a list of the most preferred R₂ substituents, wherein R=R₇=R=Y=OH; R'=R''=R'''=CH₃; and R₁=H.

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TABLE 26

R ₂	Ester Reactant (g)	A30912A Nucleus (g)	Product (g)	FABMS
H ₃ C(CH ₂) ₂ O	5.2	6.9	1.4	1142.4951**
(H ₃ C) ₃ CO(CH ₂) ₂ O	2.1	2.5	2.0	1200.5336**
H ₃ C(CH ₂) ₃ O(CH ₂) ₂ O	5.2	6.4	1.1	1194.5282*
H ₃ C(CH ₂) ₂ O	2.4	3.3	0.9	1136.4832*
(H ₃ C) ₃ CO(CH ₂) ₂ O	2.0	3.2	3.0	1194.5213*
H ₃ C(CH ₂) ₃ O	1.3	1.5	2.4	1194.5247*
H ₃ C(CH ₂) ₄ O	4.6	7.4	1.3	1126.5025*
H ₃ C(CH ₂) ₅ O	2.5	3.7	5.1	1140.5103*
(H ₃ C) ₃ CO(CH ₂) ₂ O	3.5	5.0	1.4	1154.5343*
(H ₃ C) ₃ CO(CH ₂) ₂ O	4.4	6.7	6.5	1170.5234*
(H ₃ C) ₃ CO(CH ₂) ₂ O	1.9	2.9	1.4	1170.5261*
	1.8	2.6	0.2	1166.4758*

* m+1; ** m+|Li|⁺5
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55 The N-acylhexapeptides provided by this invention are useful in the treatment of fungal infections both systemic infections and skin infections. Accordingly this invention also provides a method for treating fungal infections in man and animals which comprises administering to said host an antifungally effective non-toxic amount of an N-acyl-cyclohexapeptide represented by the formula 1. A preferred antifungal method comprises

administering an N-acylhexapeptide compound where, in formula 1, R'=R''= methyl, R₁ is hydrogen and R₂ is a preferred acyl group as defined her inabove.

The antifungal compound can be administered parenterally, e.g. i.m., i.p. or s.c., nasally, orally or can be applied topically for skin infections. The dose administered of course will vary depending on such factors as the nature and severity of the infection, the age and general health of the host and the tolerance of a particular host to the particular antifungal agent. The particular dose regimen likewise may vary according to such factors and may be given in a single daily dose or in multiple doses during the day. The regimen may last from about 2-3 days up to about 2-3 weeks or longer.

This invention also provides pharmaceutical formulations useful for administering the antifungal compounds of the invention. These formulations comprise an N-acylhexapeptide represented by the formula 1 or a pharmaceutically acceptable, non-toxic salt thereof and a pharmaceutically acceptable carrier.

For parenteral administration the formulation comprises a compound of the formula 1 and a physiologically acceptable diluent such as deionized water, physiological saline, 5% dextrose and other commonly used diluents. The formulation may contain a solubilizing agent such as a polyethylene glycol or polypropylene glycol or other known solubilizing agent. Such formulations may be made up in sterile vials containing the antifungal and excipient in a dry powder or lyophilized powder form. Prior to use, the physiologically acceptable diluent is added and the solution withdrawn via syringe for administration to the patient. For oral administration, the antifungal compound is filled into gelatin capsules or formed into tablets. Such tablets also contain a binding agent, a dispersant or other suitable excipients suitable for preparing a proper size tablet for the dosage and particular antifungal compound of the formula 1. For pediatric or geriatric use the antifungal compound may be formulated into a flavored liquid suspension, solution or emulsion. A preferred oral carrier system is lineolic acid, cremophor RH-60 and water and preferably in the amount (by volume) of 8% lineolic acid, 5% cremophor RH-60, and 87% sterile water. The compound is added to the system in an amount of 2.5 to 40 mg/ml.

For topical use the antifungal compound can be formulated with a dry powder for application to the skin surface or it may be formulated in a liquid formulation comprising a solubilizing aqueous liquid or non-aqueous liquid, e.g., an alcohol or glycol. Such formulations are useful forms for use in the antifungal method provided herein.

The N-acylcyclohexapeptides provided herein may be formulated as described above in unit dosage formulations comprising for injection between about 50 mg and about 500 mg per vial. For oral use gelatin capsules or tablets comprising between about 100 mg and about 500 mg per capsule or tablet can be provided.

Preferred formulations of the invention comprises the active ingredient presented by the formula 1 wherein R'=R''= methyl, R₁ is hydrogen and R₂ is 4-[4-(phenylethynyl)-phenyl]benzoyl in gelatin capsules or as active ingredient the antifungal represented by the formula 1 wherein R'=R''= methyl, R₁ is hydrogen and R₂ is 4-[2-(4-cyclohexyl-piperidino)ethoxy]phenyl]benzoyl or the hydrochloride salt form thereof in tablet or gelatin capsules. Further preferred formulations are those in which a preferred compound, as described above, is employed.

In yet a further aspect of the present invention there is provided a method for treating patients suffering from Pneumocystis pneumonia. The method can be used prophylactically to prevent the onset of the infection which is caused by the organism Pneumocystis carinii. The N-acylcyclicpeptide can be administered parenterally, e.g. via intramuscular (i.m.), intravenous (i.v.) or intraperitoneal (i.p.) injection, or orally or by inhalation directly into the airways of the lungs. Preferably the cyclic peptide is administered via inhalation of an aerosol spray formulation of the compound.

An effective amount of a cyclic peptide will be between about 3 mg/kg of patient body weight to about 100 mg/kg. The amount administered may be in a single daily dose or multiple doses e.g. two, three or four times daily throughout the treatment regimen. The amount of the individual doses, the route of delivery, the frequency of dosing and the term of therapy will vary according to such factors as the intensity and extent of infection, the age and general health of the patient, the response of the patient to therapy and how well the patient tolerates the drug. It is known that PCP infections in AIDS patients are highly refractory owing to the nature of the infection. For example, in severe, advanced infections the luminal surface of the air passages becomes clogged with infectious matter and extensive parasite development occurs in lung tissue. A patient with an advanced infection will accordingly require higher doses for longer periods of time. In contrast, immune deficient patients who are not severely infected and who are susceptible to PCP can be treated with lower and less frequent prophylactic doses.

The activity of the cyclicpeptide represented by the formula 1 is demonstrated in immunosuppressed rats. The tests were carried out in general as follows. One week after initiation of immunosuppression rats were inoculated intratracheally with parasites and maintained on immunosuppression for the remainder of the study. Prophylactic treatments began on day after parasite inoculation and therapeutic treatments began 3 or 4 weeks later after moderate PCP developed. Eight or ten animals were assigned to the following groups: thos

receiving test compound; non-treated Pneumocystis infected control animals; animals treated with trimethoprim-sulfamethoxazole (TMP-SMX); or non-treated, non-infected control animals. The efficacy of different treatments was evaluated by monitoring animal weights and survival during the studies and by determining the severity of PCP at necropsy. Stained impression smears of the lungs and stained lung homogenates were evaluated to determine the intensity of P. carinii infection.

The immune deficient rats employed in the tests were prepared as follows. Female Lewis rats weighing from 120-140 g each were immune suppressed with methyl prednisolone acetate at a dose of 4 mg/100 g for the first week, 3 mg/100 g for the second week and continuing weekly thereafter at 2 mg/100 g. All rats, except for the non-infected control rats, were inoculated intratracheally with 0.1 ml to 0.2 ml of Dulbecco's Modified Eagle Media containing between $>10^6$ and 10^8 P. carinii (trophozoites, precysts and cysts) harvested from the lungs of heavily infected donor animals (infection scores of 6) and maintained as cryopreserved (liquid nitrogen) inocula. Rats were maintained on immune suppression and PCP was allowed to develop for 3 or 4 weeks before initiation of therapy with test compounds. Body weights were recorded weekly and rats were allocated into treatment groups such that each group had a similar distribution of percent weight loss among animals. Rats were treated with test compounds for 2 or 3 weeks and then were necropsied. For prophylaxis studies, administration of test compound was initiated one day after intratracheal inoculation of parasites and was continued until the rats were necropsied.

Following the evaluation period for test compounds, the rats were necropsied and test results evaluated by Giemsa-stained, silver-methenamine stained impression smears and/or by silver-methenamine stained lung homogenate (see below). Necropsy was carried out as follows. The test rats were anesthetized with a mixture of ketamine hydrochloride and xylazine and then exsanguinated via the right atrium. Internal organs in the abdominal and thoracic cavities were examined for gross lesions.

A small portion of lung tissue from the left lobe of each rat was used to make the impression smears described below. Giemsa-stained impression smears were evaluated to determine the total number of parasites (trophozoites, precysts, and cysts). Impression smears from rats in groups whose treatments exhibited some anti-Pneumocystis activity (as judged by infection scores from Giemsa-stained slides) and from rats in the control groups were also stained with methenamine silver, a stain specific for the cyst wall of the organism. Impression smears were randomized, numbered, and then evaluated. The infection scores used were as follows:

Score	Basis
0	No parasites found
1	1 to 5 parasites/10 oil fields
2	ca 1 parasite/field
3	2-10 parasites/field
4	>10 but <100 parasites/field
5	>100 but <1,000 parasites/field

A score of 6 was reserved for those infections with impression smears containing $>1,000$ organisms/field (too numerous to count). Giemsa-stained slides were examined microscopically using a final magnification of 1008X. Methenamine silver-stained slides were examined with a final magnification of 400X.

Cysts in rat lung tissue were quantified as follows. A small portion of lung tissue from the left lobe of each rat was used to make impression smears as described above. The remainder of each lung was weighed, placed in a tube containing Hanks balanced salt solution (HBSS) (40X the lung weight) and homogenized using a Biinkman model tissue homogenizer. Two μ l samples of the homogenized lung samples (1:4 dilution in HBSS) were placed in wells of teflon-coated, 12-well slides, stained with methenamine silver, and the number of cysts were scored as described above for the impression smears.

The activity and efficacy of two preferred N-acylcyclohexapeptides in the test animals is presented below. The compound of the formula 1 wherein R'=R''= methyl, R₁ is hydrogen and R₂ is 4[(4-phenylethynyl)phenyl]benzoyl when administered as an aerosol solution at a concentration of 5 mg/ml for one hour, twice weekly for 5 weeks resulted in 90% reduction in P. carinii cysts in the lungs. When given orally at 10 mg/kg, bid for 3 weeks, the number of cysts in the lungs was reduced by >99% when compared with infected vehicle controls.

When the preferred N-acylcyclic peptides were administered orally and by intraperitoneal injection the compound was effective in clearing P. carinii cysts from the lungs of heavily infected rats. For example, when th

comp und was administered at 10 or 40 mg/kg, bid for 4, 8 or 12 days, the number of identifiabl cysts in the lungs of heavily infected rats was reduced by >99%. Similar efficacy was observed when the compound was administered i.p. at 1 mg/kg.

When tested orally for prophylactic activity, the preferred compound exhibited >99% cyst reduction in one of two studies when infected animals were dosed at 1 mg/kg and when given higher doses of 5 or 4 mg/kg.

Another preferred compound of the invention represented by the formula 1 wherein R'=R''= methyl, R₁ is hydrogen and R₂ is 4-[2-(4-cyclohexyl(piperidino)ethoxy]phenyl]benzoyl as the hydrochloride salt was also effective in the treatment of PCP. Aerosol prophylaxis (two 60-minute treatments twice a week for 5 weeks) was highly effective. in preventing PCP in the infected immune suppressed rats. Aerosol therapy with 5, 10, 10 25, or 50 mg/ml of aerosolized solution reduced the number of cysts in the lungs by >99% when compared to controls. Similar results were obtained by i.p. dosage.

The following examples of compounds of the invention and the manner of their preparation further describe the present invention.

15 N-Acylation of Cyclohexapeptide Nuclei

The preparation of the derivatives of the A30912A nucleus was accomplished by the following general procedure, with Table 27 listing these derivatives.

The A30912A nucleus and the 2,4,5-trichlorophenol ester are dissolved in dimethylformamide (25-50 ml) and stirred for 17-65 hours at room temperature. The solvent is removed *in vacuo* and the residue is slurried in ether and collected by filtration. The solid product is washed with methylene chloride and then dissolved in either methanol or acetonitrile/water (1:1 v/v). This solution is injected on a Waters 600E semi-preparative chromatography system using a Rainin Dynamax-60A C₁₈ reverse-phase column. The column is eluted beginning with 20-40% aqueous acetonitrile and 0.5% monobasic ammonium phosphate (w/v) (monitored by UV at 230 nm and at a flow rate of 20 ml/min) until the unreacted A30912A nucleus is eluted and then deleting the buffer and eluting the product peak in aqueous acetonitrile. The fraction containing the product is evaporated *in vacuo* or lyophilized to provide the pure compound. The product may be analyzed by the same HPLC instrument using a Waters C₁₈ Micro Bondapak column and eluting with 40% aqueous acetonitrile containing 0.5% monobasic ammonium phosphate (w/v) at a 2 ml/min flow rate and monitoring the UV at 230 nm. The products may also be analyzed by fast atom bombardment mass spectrometry (FABMS). (In the compounds used, R'=R''=CH₃, R=OH, RY=OH, R₁=H, R₇=OH, and R₂ is as defined).

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TABLE 27

R ₂	Reagent Reactant (mM)	Ester A30912A Nucleus (g)	Product (mg)	FABMS	HPLC Retention (min)
<chem>CC(C)C(C)COc1ccc(cc1)Oc2ccc(cc2)O</chem>	561	1.0	235	1072*	4.08
<chem>C1CCC1Cc2ccc(cc2)Oc3ccc(cc3)O</chem>	576	1.0	294	1062*	4.46
<chem>CC(C)C(C)COc1ccc(cc1)Oc2ccc(cc2)Oc3ccc(cc3)O</chem>	579	1.0	355	1086*	5.75
<chem>CC(C)C(C)COc1ccc(cc1)Oc2ccc(cc2)Oc3ccc(cc3)Oc4ccc(cc4)O</chem>	614	1.0	359	1130*	5.79
<chem>CC(C)C(C)COc1ccc(cc1)Oc2ccc(cc2)Oc3ccc(cc3)Oc4ccc(cc4)Oc5ccc(cc5)O</chem>	289	0.5	81	1083*	6.08
<chem>C1CCCC1Cc2ccc(cc2)Oc3ccc(cc3)Oc4ccc(cc4)Oc5ccc(cc5)O</chem>	594	1.0	295	1098*	6.44
<chem>CC(C)C(C)COc1ccc(cc1)Oc2ccc(cc2)Oc3ccc(cc3)Oc4ccc(cc4)Oc5ccc(cc5)Oc6ccc(cc6)O</chem>	596	1.0	270	1100*	8.15
<chem>CC(C)C(C)COc1ccc(cc1)Oc2ccc(cc2)Oc3ccc(cc3)Oc4ccc(cc4)Oc5ccc(cc5)Oc6ccc(cc6)Oc7ccc(cc7)O</chem>	596	1.0	359	1100*	9.13
<chem>CC(C)C(C)COc1ccc(cc1)Oc2ccc(cc2)Oc3ccc(cc3)Oc4ccc(cc4)Oc5ccc(cc5)Oc6ccc(cc6)Oc7ccc(cc7)Oc8ccc(cc8)O</chem>	596	1.0	301	1100*	10.24
<chem>C1CCCC1Cc2ccc(cc2)Oc3ccc(cc3)Oc4ccc(cc4)Oc5ccc(cc5)Oc6ccc(cc6)Oc7ccc(cc7)Oc8ccc(cc8)O</chem>	629	1.0	180	1104**	
<chem>CC(C)C(C)COc1ccc(cc1)Oc2ccc(cc2)Oc3ccc(cc3)Oc4ccc(cc4)Oc5ccc(cc5)Oc6ccc(cc6)Oc7ccc(cc7)Oc8ccc(cc8)Oc9ccc(cc9)O</chem>	683	1.0	384	1147**	1.92
<chem>CC(C)C(C)COc1ccc(cc1)Oc2ccc(cc2)Oc3ccc(cc3)Oc4ccc(cc4)Oc5ccc(cc5)Oc6ccc(cc6)Oc7ccc(cc7)Oc8ccc(cc8)Oc9ccc(cc9)Oc10ccc(cc10)O</chem>	1490	2.0	116	1195**	2.06
<chem>CC(C)C(C)COc1ccc(cc1)Oc2ccc(cc2)Oc3ccc(cc3)Oc4ccc(cc4)Oc5ccc(cc5)Oc6ccc(cc6)Oc7ccc(cc7)Oc8ccc(cc8)Oc9ccc(cc9)Oc10ccc(cc10)Oc11ccc(cc11)O</chem>	1000	1.2	194	1190**	2.41

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TABLE 27 continued

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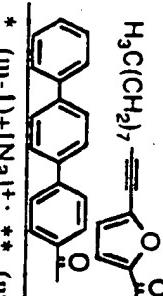
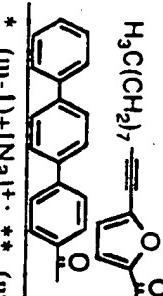
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TABLE 27 continued

R2					
	Ester Reactant (mg)	A30912A Nucleus (g)	Product (mg)	FABMS	HPLC Retention (min)
	534	1.0	215	1050***	7.59
	566	1.0	81	1054**	3.89

50 Compounds such as those listed in Table 27 could be further modified at the phenolic hydroxy to provide R7 = -OPO₃HNa as shown in Table 28. The procedure is as follows:

The lipopeptide (1 equivalent) and tetrabenzylpyrophosphate (2 equivalents) were dissolved in dimethylformamide which had been dried over 13X molecular sieves. Lithium hydroxide monohydrate (5 equivalents) was added and the stirred solution was monitored by HPLC. After 0.5 hr and 1 hr more lithium hydroxide (5 equivalents) was added. Between 1 and 2 hrs. the reaction was quenched with glacial acetic acid, the solvent removed under vacuum, and the residue purified over a semi-preparative C18 reverse-phase column using an aqueous acetonitrile eluent. The purified product was dissolved in (1/1) acetic acid/water with sodium acetate (1 equivalent) and 10% Pd/C catalyst. The solution was placed under an atmosphere of hydrogen gas and

stirred for 1 hr. After filtering to remove the catalyst, the solution was lyophilized to provide the pure final product. The purity was assessed by analytical HPLC and the product was analyzed by fast atom bombardment mass spectrometry (FABMS).

R ₂	Start. Mat.	Wt. (mg)	Prod.	Wt. (mg)	FABMS
<chem>*c1ccccc1CCc2ccc(O)cc2</chem>	-OH R ₇	500	-OP(O)HNa R ₇	140	1184
<chem>*c1ccc(cc1OCC(C)C)c2ccc(O)cc2</chem>	-OH	300	-OP(O)HNa	62	1228.4472*
* m+1					

Preparation of dideoxy cyclohexapeptide

The preparation of the dideoxy compounds may be accomplished by the following procedure with Table 29 listing derivatives.

- 5 To a suspension of a non-dideoxy cyclohexapeptide (formula (I) where R=OH and R₂ is hydrogen or acyl), in dichloromethane is added the reducing agent triethylsilane in dichloromethane. The solution is stirred and the volatile components are removed under reduced pressure and the residue triturated with diethyl ether. The compound is purified using HPLC, and the product lyophilized.

10 Example

Dideoxycilofungin

- 15 To a suspension of cilofungin (10.00 g, 9.71 mmol) in dichloromethane (100 ml) was added a solution of triethylsilane (96 ml, 602 mmol) in dichloromethane (50 ml). Trifluoroacetic acid (46.4 ml, 602 mmol) was added as a solution in dichloromethane (50 ml) over 15 minutes. The solution was stirred at room temperature for two hours. The volatile reaction components were removed under reduced pressure and the residue triturated with diethyl ether. The compound was purified by reversed phase HPLC by means of a "Prep LC/System 500" unit (Waters Associates, Inc., Milford, Mass.) using a Prep Pak 500/C₁₈ Column (Waters Associates, Inc.) as 20 the stationary phase. The column eluted with a gradient mobile phase using CH₃CN/H₂O (10:90 to 20:80 v/v) at 500 psi. The product containing fractions were pooled, evaporated under reduced pressure, and lyophilized from p-dioxane to yield dideoxycilofungin (6.66 g, 68.7%). FAB-MS: m/z calc. for C₄₉H₇₂N₇O₁₅, 998.5086; found, 998.512; UVλ(EtOH)nm(ε) 202.60(61012), 256.20(18569).

- 25 Table 29, indicates R₂, the amount of the cyclic hexapeptide and reagents, and yield of dideoxy compounds prepared as described above. (R'=R''=R'''=CH₃, R₁=H and R=R''=R'''=OH); T.E.S. = triethylsilane; TFA=trifluoroacetic acid; numbers are weights in grams).

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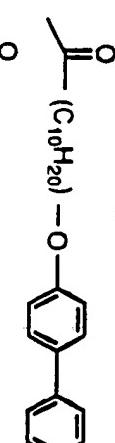
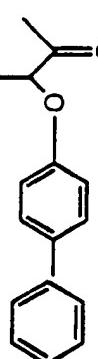
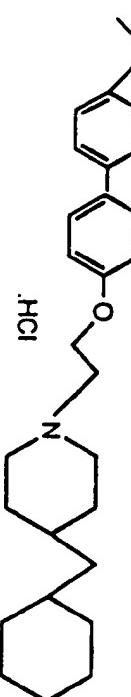
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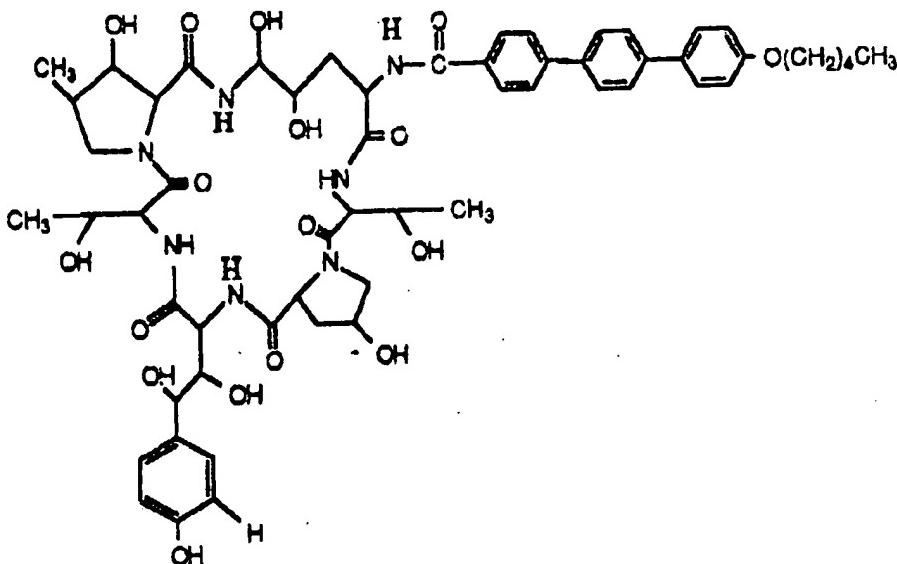
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Table 29

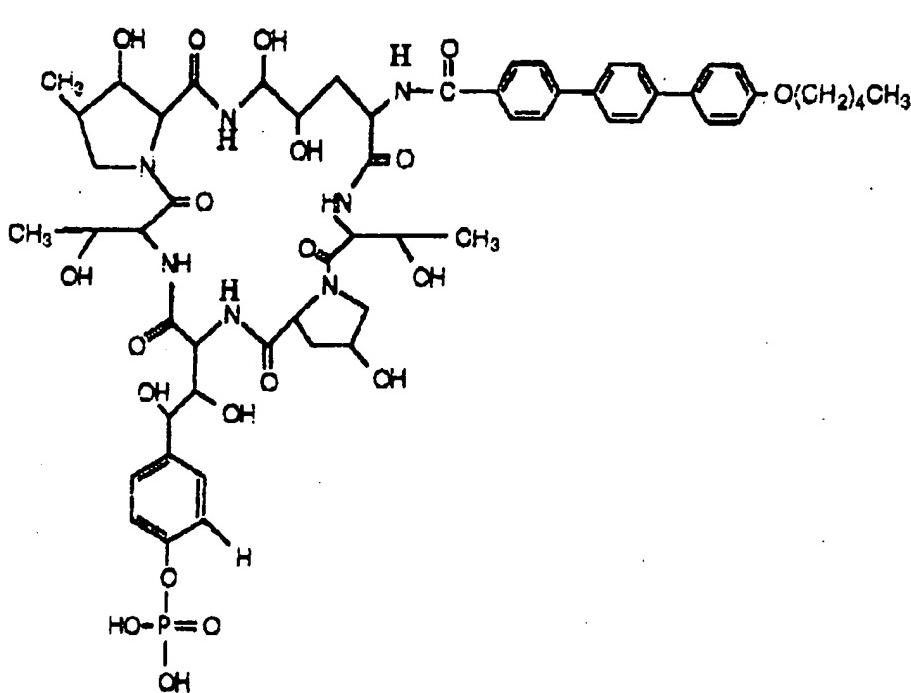
	R ₂	Starting Material	TES	TEA	Yield
5			0.500	0.256	0.251
10					0.095
15			0.500	2.47	2.42
20					0.063
25			0.500	2.63	2.57
30					0.392
35			2.00	9.49	9.72
40					1.47
45			0.500	3.50	3.44
50					0.291

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A compound of the formula



the preparation of which is discussed just prior to Table 27, can also be further modified at the phenolic hydroxy to provide R₇=-OPO₃HNa, as indicated in the two paragraphs prior to Table 28. The compound produced is as follows:

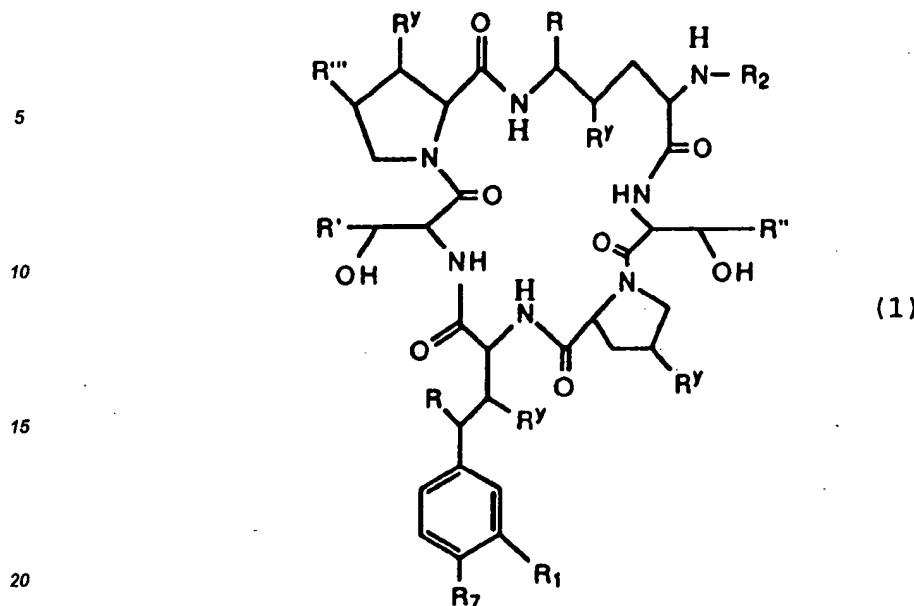


50 The product was analyzed by FABMS (using Lit) to give a peak at 1226.4853 (calculated for C₅₈H₇₄N₇O₂₀PLi=1226.4886). Also, when analyzed by HPLC using a C18 reverse-phase column and eluting with 55% aqueous acetonitrile with 0.5% acetic acid at 2 ml/min and monitoring by UV at 280 nm, the compound had a retention time of 1.72 min.

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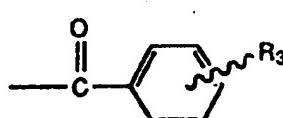
Claims

1. A compound of the formula (1):



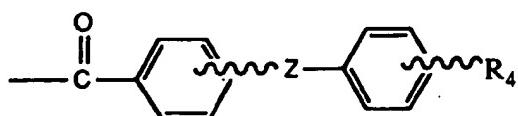
wherein

- 25
- R' is hydrogen, methyl or $\text{NH}_2\text{C}(\text{O})\text{CH}_2\text{-}$;
 - R'' and R''' are independently methyl or hydrogen;
 - R and R^Y are independently hydroxy or hydrogen;
 - R₁ is hydroxy, hydrogen, or hydroxysulfonyloxy;
 - R₇ is hydroxy, hydrogen, hydroxysulfonyloxy or phosphonoxy; and
- 30
- I) R₂ is a substituted benzoyl group represented by the formula



wherein

- A) R₃ is a polyoxa-alkyl group represented by the formula
 $-\text{O}-(\text{CH}_2)_m-\text{[O}-(\text{CH}_2)_n\text{]}_p-\text{O}-(\text{C}_1\text{-C}_{12}\text{ alkyl})$
- 40
- wherein m and n are integers of from 2 to 4, and p is 0 or 1; or
- B) R₃ is an unsaturated hydrocarbon group represented by the formula
 $-\text{Y}-(\text{C}_1\text{-C}_{12}\text{ alkyl})$
- 45
- wherein Y is -C≡C- or -CH=CH-; or
- C) R₃ is a group of the formula -O-(CH₂)_m-G, wherein m is as defined and G is C₇-C₁₀ bicycloalkyl or C₇-C₁₄ tricycloalkyl; or
- D) R₃ is quinolyl; or
- II) R₂ is an acyl group represented by the formula

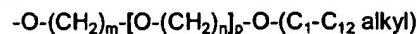


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- Z is -O-, -C≡C-, -CH=CH-, -CH₂-CH₂-, -CH₂- or a carbon to carbon bond;
- A) R₄ is hydrogen, C₂-C₁₂ alkynyl, C₂-C₁₂ substituted alkynyl, C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, C₁-C₁₂ alkoxy, C₃-C₁₂ cycloalkoxy, naphthyl, pyridyl, thiienyl, benzothienyl, qui-

nolyl or phenyl; or

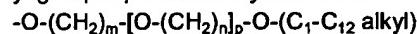
B) R₄ is phenyl substituted by amino, C₁-C₁₂ alkylthio, halogen, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₁-C₁₂ substituted alkyl, C₂-C₁₂ substituted alkenyl, C₂-C₁₂ substituted alkynyl, C₁-C₁₂ alkoxy, trifluoromethyl, phenyl, substituted phenyl, phenyl substituted with a polyoxa-alkyl group represented by the formula



wherein m,n and p are as defined; or

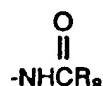
C) R₄ is phenyl substituted with C₁-C₆ alkoxy substituted by fluoro, bromo, chloro or iodo; or

D) R₄ is C₁-C₁₂ alkoxy substituted with C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, C₂-C₁₂ alkynyl, amino, C₁-C₄ alkylamino, di-(C₁-C₄ alkyl)amino, C₁-C₁₂ alkanoylamino, phenyl substituted with a polyoxa-alkyl group represented by the formula



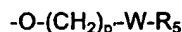
wherein m,n and p are as defined; or

E) R₄ is C₁-C₁₂ alkoxy substituted with a group of the formula



wherein R₈ is C₁-C₆ alkoxy optionally substituted with phenyl; or

F) R₄ is a group represented by the formula



wherein p' is an integer of from 2 to 4; W is pyrrolidino, piperidino or piperazino, and R₅ is hydrogen, C₁-C₁₂ alkyl, C₃-C₁₂ cycloalkyl, benzyl or C₃-C₁₂ cycloalkylmethyl; or

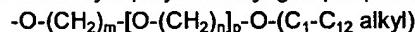
G) R₄ is a group represented by the formula



wherein Y has the same meanings defined above; and

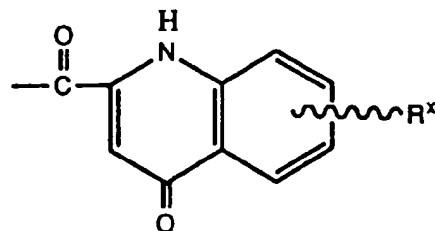
R₆ is C₁-C₁₂ alkyl, C₁-C₁₂ substituted alkyl; C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, phenyl, C₃-C₁₂ cycloalkenyl, naphthyl, benzothiazolyl, thienyl, phenyl substituted by amino, C₁-C₁₂ alkylthio, halogen, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₁-C₁₂ alkoxy, trifluoromethyl, -O-(CH₂)_{p'}-W-R₅, or C₁-C₆ alkoxy substituted by fluoro, bromo, iodo or chloro; or

R₆ is a phenyl substituted by a polyoxa-alkyl group represented by the formula

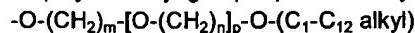


wherein m,n and p are as defined above; or

III) R₂ is a group having the formula



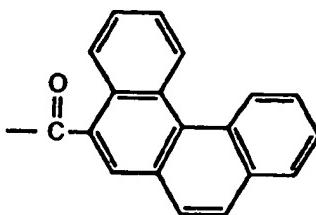
wherein R^x is C₁-C₁₂ alkoxy or a polyoxa-alkyl group represented by the formula



wherein m,n and p are as defined above; or

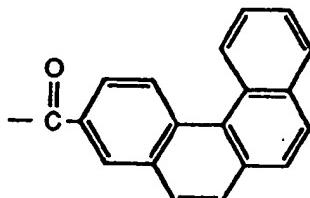
IV) R₂ is a group having the formula

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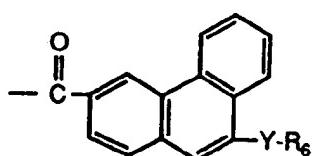
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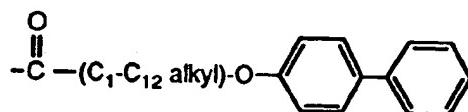


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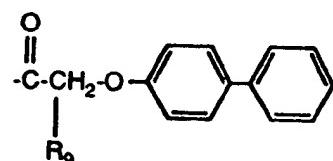


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wherein R₉ is phenyl, C₁-C₁₂ alkyl, or C₁-C₁₂ alkoxy; or
V) R₂ is naphthoyl substituted with R₄; and the pharmaceutically acceptable non-toxic salts thereof;

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with the proviso that when

R' is methyl or NH₂C(O)CH₂;

R'' is methyl;

R''' is methyl;

R^Y is hydroxy;

R is hydroxy; and

either a) or b):

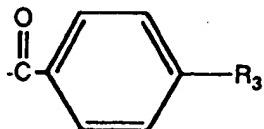
a) R₁ is hydroxysulfonyloxy and R₇ is hydroxy, hydroxysulfonyloxy or phosphonoxy;

b) R₁ is hydrogen or hydroxysulfonyloxy and R₇ is hydroxysulfonyloxy or phosphonoxy;

R₂ is not

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i)



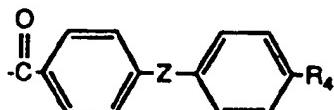
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wherein R_3 is

-O-(CH₂)_m-[O-(CH₂)_n]_p-O-(C₁-C₁₂ alkyl)

wherein $p=0$; nor

ii)

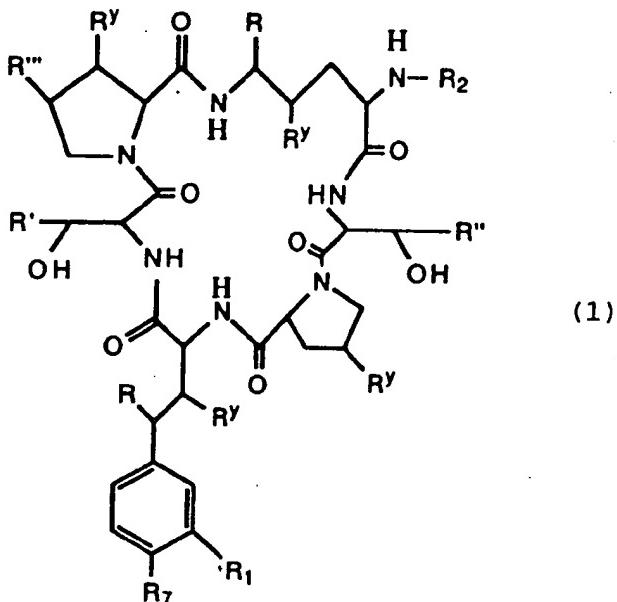


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wherein Z is a carbon to carbon bond or -O- and R₄ is C₁-C₁₂ alkoxy; nor
iii) naphthoyl substituted by R₄ wherein R₄ is hydrogen, phenyl, or C₁-C₁₂ alkoxy.

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2. A compound of the formula (1):



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wherein

R' is hydrogen, methyl or $\text{NH}_2\text{C}(\text{O})\text{CH}_2$ -;

R" and R'" are independently methyl or hydrogen;

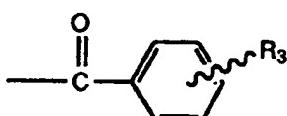
R and R^Y are independently hydroxy or hydrogen;

R_1 is hydroxy or hydrogen;

R_2 is hydroxy or hydrogen; and

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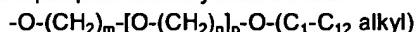
1) R₂ is a substituted benzoyl group represented by the formula



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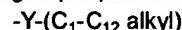
wherein

A) R_3 is a polyoxa-alkyl group represented by the formula



wherein m and n are integers of from 2 to 4, and p is 0 or 1; or

B) R_3 is an unsaturated hydrocarbon group represented by the formula



wherein Y is $-\text{C}\equiv\text{C}-$ or $-\text{CH}=\text{CH}-$; or

C) R_3 is a group of the formula $-\text{O}-(\text{CH}_2)_m-\text{G}$, wherein m is as defined and G is $\text{C}_7\text{-C}_{10}$ bicycloalkyl or $\text{C}_7\text{-C}_{14}$ tricycloalkyl; or

D) R_3 is quinolyl; or

II) R_2 is an acyl group represented by the formula

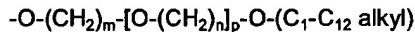


wherein

20 Z is $-\text{O}-$, $-\text{C}\equiv\text{C}-$, $-\text{CH}=\text{CH}-$, $-\text{CH}_2\text{-CH}_2-$, $-\text{CH}_2-$, or a carbon to carbon bond;

A) R_4 is hydrogen, $\text{C}_2\text{-C}_{12}$ alkynyl, $\text{C}_2\text{-C}_{12}$ substituted alkynyl, $\text{C}_3\text{-C}_{12}$ cycloalkyl, $\text{C}_7\text{-C}_{10}$ bicycloalkyl, $\text{C}_7\text{-C}_{14}$ tricycloalkyl, $\text{C}_1\text{-C}_{12}$ alkoxy, $\text{C}_3\text{-C}_{12}$ cycloalkoxy, naphthyl, pyridyl, thienyl, benzothienyl, quinolyl or phenyl; or

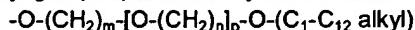
B) R_4 is phenyl substituted by amino, $\text{C}_1\text{-C}_{12}$ alkylthio, halogen, $\text{C}_1\text{-C}_{12}$ alkyl, $\text{C}_2\text{-C}_{12}$ alkenyl, $\text{C}_2\text{-C}_{12}$ alkynyl, $\text{C}_1\text{-C}_{12}$ substituted alkyl, $\text{C}_2\text{-C}_{12}$ substituted alkenyl, $\text{C}_2\text{-C}_{12}$ substituted alkynyl, $\text{C}_1\text{-C}_{12}$ alkoxy, trifluoromethyl, phenyl, substituted phenyl, phenyl substituted with a polyoxa-alkyl group represented by the formula



wherein m,n and p are as defined; or

C) R_4 is phenyl substituted with $\text{C}_1\text{-C}_6$ alkoxy substituted by fluoro, bromo, chloro or iodo; or

D) R_4 is $\text{C}_1\text{-C}_{12}$ alkoxy substituted with $\text{C}_3\text{-C}_{12}$ cycloalkyl, $\text{C}_7\text{-C}_{10}$ bicycloalkyl, $\text{C}_7\text{-C}_{14}$ tricycloalkyl, $\text{C}_2\text{-C}_{12}$ alkynyl, amino, $\text{C}_1\text{-C}_4$ alkylamino, di-($\text{C}_1\text{-C}_4$ alkyl)amino, $\text{C}_1\text{-C}_{12}$ alkanoylamino, phenyl substituted with a polyoxa-alkyl group represented by the formula



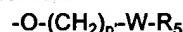
35 wherein m,n and p are as defined; or

E) R_4 is $\text{C}_1\text{-C}_{12}$ alkoxy substituted with a group of the formula



wherein R_8 is $\text{C}_1\text{-C}_6$ alkoxy optionally substituted with phenyl; or

F) R_4 is a group represented by the formula



45 wherein p' is an integer of from 2 to 4; W is pyrrolidino, piperidino or piperazino, and R_5 is hydrogen, $\text{C}_1\text{-C}_{12}$ alkyl, $\text{C}_3\text{-C}_{12}$ cycloalkyl, benzyl or $\text{C}_3\text{-C}_{12}$ cycloalkylmethyl; or

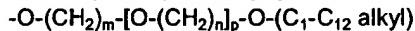
G) R_4 is a group represented by the formula



wherein Y has the same meanings defined above; and

50 R_6 is $\text{C}_1\text{-C}_{12}$ alkyl, $\text{C}_1\text{-C}_{12}$ substituted alkyl; $\text{C}_3\text{-C}_{12}$ cycloalkyl, $\text{C}_7\text{-C}_{10}$ bicycloalkyl, $\text{C}_7\text{-C}_{14}$ tricycloalkyl, phenyl, $\text{C}_3\text{-C}_{12}$ cycloalkenyl, naphthyl, benzothiazolyl, thienyl, phenyl substituted by amino, $\text{C}_1\text{-C}_{12}$ alkylthio, halogen, $\text{C}_1\text{-C}_{12}$ alkyl, $\text{C}_2\text{-C}_{12}$ alkenyl, $\text{C}_2\text{-C}_{12}$ alkynyl, $\text{C}_1\text{-C}_{12}$ alkoxy, trifluoromethyl, $-\text{O}-(\text{CH}_2)_p-\text{W-R}_5$, or $\text{C}_1\text{-C}_6$ alkoxy substituted by fluoro, bromo, iodo or chloro; or

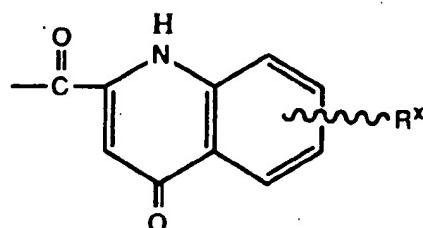
R_6 is a phenyl substituted by a polyoxa-alkyl group represented by the formula



55 wherein m,n and p are as defined above; or

III) R_2 is a group having the formula

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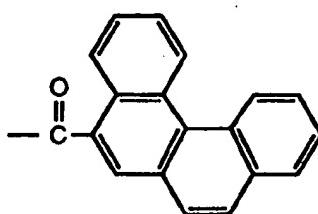
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wherein R^x is C₁-C₁₂ alkoxy or a polyoxa-alkyl group represented by the formula
 $-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12} \text{ alkyl})$

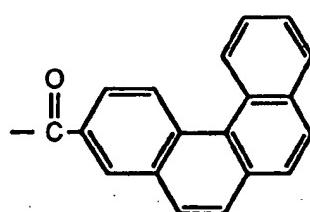
wherein m,n and p are as defined above; or

IV) R₂ is a group having the formula

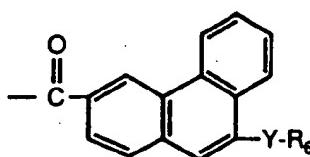
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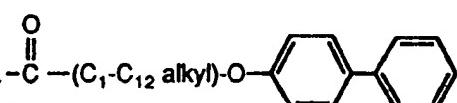


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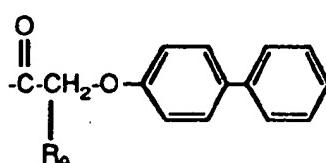
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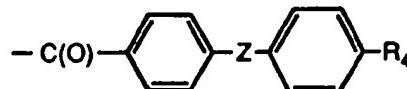


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wherein R₉ is phenyl, C₁-C₁₂ alkyl, or C₁-C₁₂ alkoxy; or
 V) R₂ is naphthoyl substituted with R₄; and the pharmaceutically acceptable non-toxic salts thereof.

3. A compound as recited in Claims 1 or 2 wherein R', R'' and R''' are methyl, R₁ is hydrogen, and R₇ and R^Y are OH.
4. A compound as recited in Claims 1 or 2 wherein R₂ is of the formula

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wherein Z is a carbon to carbon bond; and

R₄ is C₁-C₁₂ alkoxy, C₃-C₇ cycloalkoxy, C₁-C₈ alkoxy substituted by C₃-C₇ cycloalkyl; or

R₄ is phenyl substituted by C₁-C₁₂ alkoxy or phenyl substituted with a polyoxa-alkyl group of the formula

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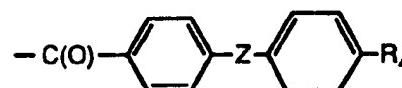
-O-(CH₂)_m-[O-(CH₂)_n]P-O-(C₁-C₁₂ alkyl); or

R₄ is a group of the formula -Y-R₆, wherein Y is an acetylenic bond and R₆ is C₁-C₆ alkyl, phenyl, or phenyl substituted with a polyoxa-alkyl group of the formula

-O-(CH₂)_m-[O-(CH₂)_n]P-O-(C₁-C₁₂ alkyl).

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5. A compound as recited in claims 1 or 2 wherein R₂ is of the formula



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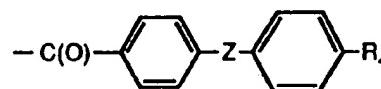
wherein Z is -C≡C- ; and

R₄ is phenyl substituted by C₁-C₁₂ alkoxy or phenyl substituted with a polyoxa-alkyl group of the formula

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-O-(CH₂)_m-[O-(CH₂)_n]P-O-(C₁-C₁₂ alkyl)

6. A compound as recited in Claims 1 or 2 wherein R₂ is of the formula



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wherein Z is a carbon to carbon bond and R₄ is a group of the formula

-O-(CH₂)_p-W-R₅

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wherein W is a piperidine group.

7. A compound as recited in Claims 1 or 2 wherein R is hydrogen.

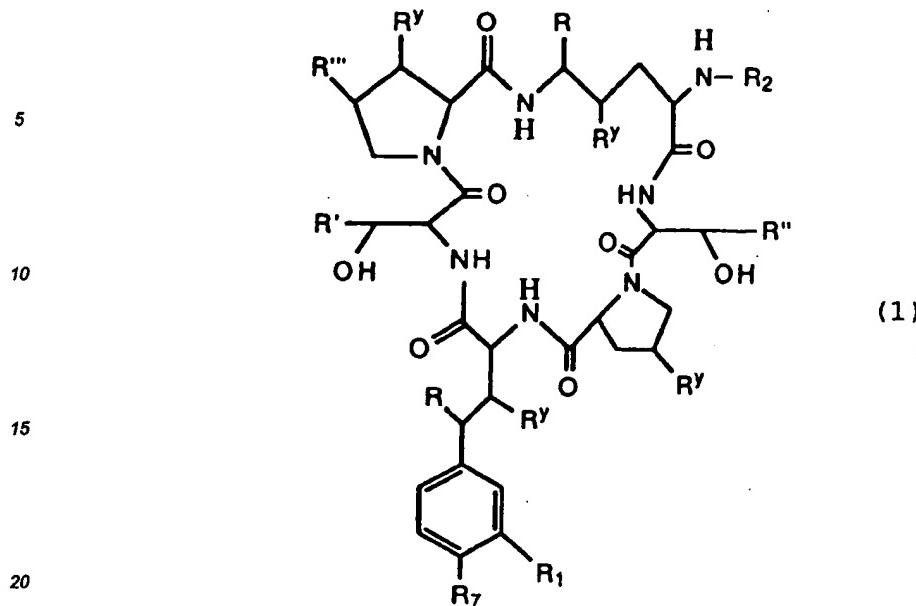
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8. A compound as recited in claims 1 or 2 wherein R₂ is 4-(4-n-hexyloxyphenyl)benzoyl, 4-(4-n-heptyloxyphenyl)benzoyl, 4-(4-n-octyloxyphenyl)benzoyl, 4-[4-(3,3-dimethylbutoxy)phenyl]benzoyl, 4-[4-(2-cyclopentylethoxy)phenyl]benzoyl, 4-[4-(2-cyclohexyloxyethoxy)phenyl]benzoyl, 4-[4-(phenylethynyl)phenyl]benzoyl, 4-[4-(n-butylethynyl)phenyl]benzoyl, or 4-[4-[2-(4-cyclohexyl)piperidino]ethoxy]phenyl]benzoyl.

9. A compound of the formula (1):

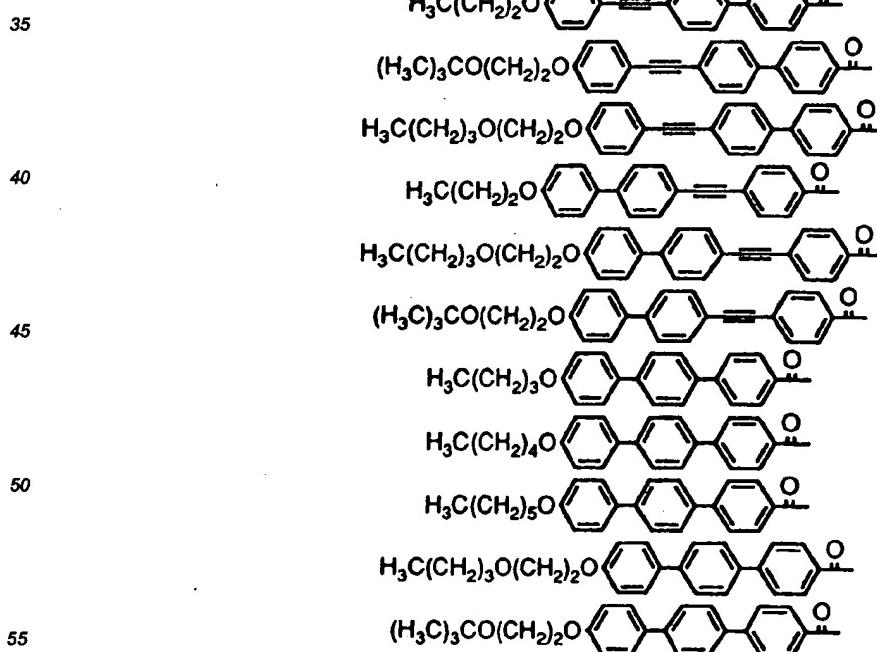
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wherein

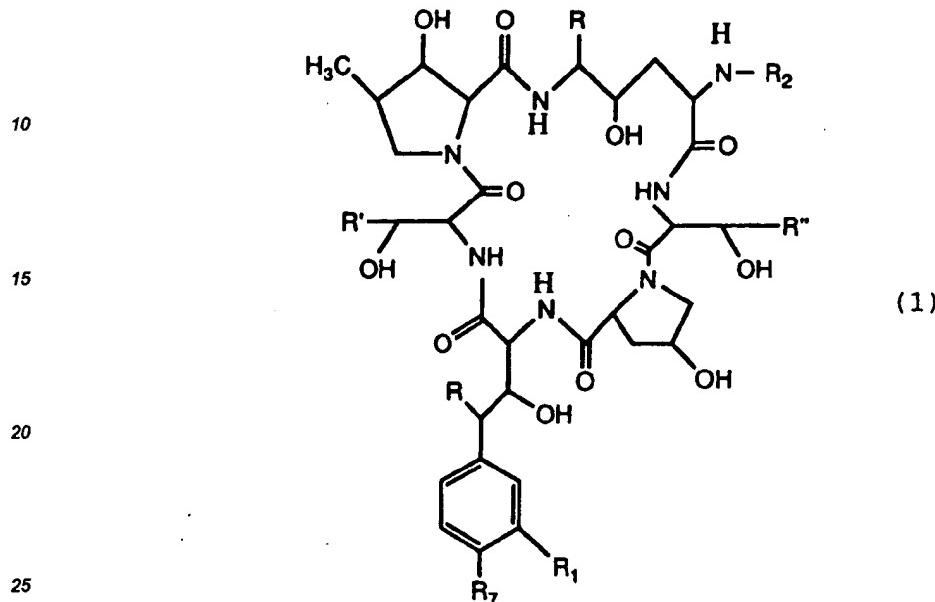
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- R' is hydrogen, methyl or $\text{NH}_2\text{C}(\text{O})\text{CH}_2\text{-}$;
 - R'' and R''' are independently methyl or hydrogen;
 - R and R^Y are independently hydroxy or hydrogen;
 - R₁ is hydroxy, hydrogen, or hydroxysulfonyloxy;
 - R₇ is hydroxy, hydrogen, hydroxysulfonyloxy or phosphonoxy; and
 - I) R₂ is a group of the formula
- 30



R', R'' and R''' are methyl, R₁ is hydrogen and R₇ and R^Y are hydroxy and pharmaceutically acceptable salts thereof.

10. A compound of the formula (1):

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wherein R' is hydrogen, methyl or NH₂C(O)CH₂;

R'' is methyl or hydrogen;

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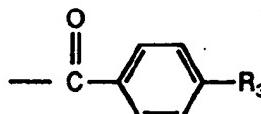
R is hydroxy or hydrogen;

R₁ is hydroxy, hydrogen, or hydroxysulfonyloxy;

R₇ is hydroxy, hydrogen, hydroxysulfonyloxy or phosphonoxy;

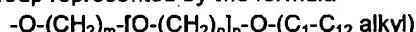
R₂ is a substituted benzoyl group represented by the formula

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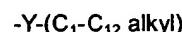
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wherein R₃ is a polyoxa-alkyl group represented by the formula



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wherein m and n are integers of from 2 to 4, and p is 0 or 1; or R₃ is an unsaturated hydrocarbon group represented by the formula



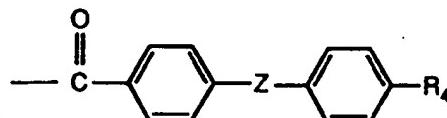
wherein Y is -C≡C- or -CH=CH-;

or R₃ is a group of the formula -O-(CH₂)_m-G, wherein m is as defined and G is C₇-C₁₀ bicycloalkyl or C₇-C₁₄ tricycloalkyl;

50

or R₂ is an acyl group represented by the formula

55



wherein Z is -O-, -C≡C-, -CH=CH-, -CH₂-CH₂-, or a carbon to carbon bond;

R₄ is hydrogen, C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, phenyl, phenyl substituted by amino, C₁-C₁₂ alkylthio, halogen, C₁-C₁₂ alkyl, C₁-C₁₂ alkoxy, trifluoromethyl, ph nyl, or C₁-C₆ alkoxy substituted by fluoro, bromo, chloro or iodo;

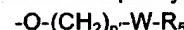
5 or R₄ is C₁-C₁₂ alkoxy, C₃-C₁₂ cycloalkoxy, C₁-C₁₂ alkoxy substituted by C₃-C₁₂ cycloalkyl, C₇-C₁₀ bicycloalkyl, C₇-C₁₄ tricycloalkyl, amino, C₁-C₄ alkylamino, di-(C₁-C₄ alkyl)amino, C₁-C₁₂ alkanoylamino or a group of the formula

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wherein R₈ is C₁-C₆ alkoxy optionally substituted with phenyl; or R₄ is a group represented by the formula

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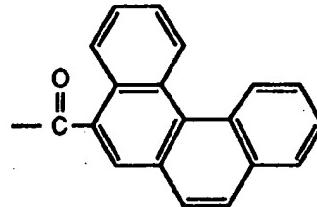
wherein p' is an integer of from 2 to 4; W is pyrrolidino, piperidino or piperazino, and R₅ is hydrogen, C₁-C₁₂ alkyl, C₃-C₁₂ cycloalkyl, benzyl or C₃-C₁₂ cycloalkylmethyl;

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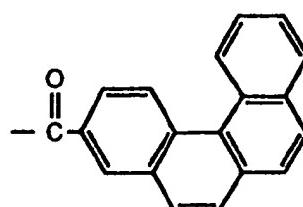
or R₄ is a group represented by the formula -Y-R₆ wherein Y has the same meanings defined above and R₆ is C₁-C₁₂ alkyl, C₁-C₁₂ alkyl substituted by phenyl; C₃-C₁₂ cycloalkyl, phenyl, C₃-C₁₂ cycloalkenyl, naphthyl, benzthiazol-2-yl, or phenyl substituted by amino, C₁-C₁₂ alkylthio, halogen, C₁-C₁₂ alkyl, C₁-C₁₂ alkenyl, C₁-C₁₂ alkoxy, trifluoromethyl, -O-(CH₂)p'-W-R₆, or C₁-C₆ alkoxy substituted by fluoro, bromo, iodo or chloro; or

R₂ is a group selected from

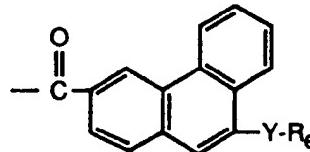
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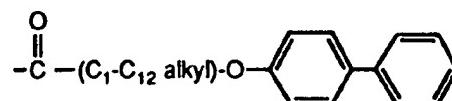
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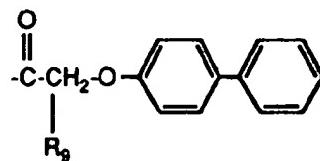
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wherein R₉ is phenyl, C₁-C₁₂ alkyl, or C₁-C₁₂ alkoxy; or
R₂ is naphthoyl substituted with R₄; and the pharmaceutically acceptable non-toxic salts thereof;

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with the proviso that when

R' is methyl or NH₂C(O)CH₂-;

R" is methyl;

R is hydroxy; and

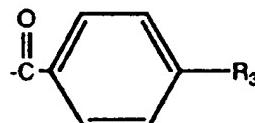
either

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- a) R₁ is hydroxysulfonyloxy and R₇ is hydroxy, hydroxysulfonyloxy or phosphonoxy; or
- b) R₁ is hydrogen or hydroxysulfonyloxy and R₇ is hydroxysulfonyloxy or phosphonoxy;
R₂ is not

i)

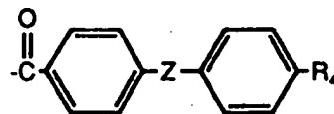
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wherein R₃ is -O-(CH₂)_m-[O-(CH₂)_n]_p-O-(C₁-C₁₂ alkyl) wherein p=0; nor
ii)

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wherein Z is a carbon to carbon bond or -O- and R₄ is C₁-C₁₂ alkoxy; nor
iii) naphthoyl substituted by R₄ wherein R₄ is hydrogen, phenyl, or C₁-C₁₂ alkoxy.

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11. A compound as recited in claim 10 wherein R₁ is not hydroxysulfonyloxy and R₇ is not hydroxysulfonyloxy or phosphonoxy.

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12. A compound of any of claims 1-11 for use in inhibiting parasitic activity.

13. A compound of claims 1-11 for use in inhibiting fungal activity.

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14. A compound of any of claims 1-11 for use in inhibiting the growth of organisms responsible for opportunistic infections in immunosuppressed individuals.

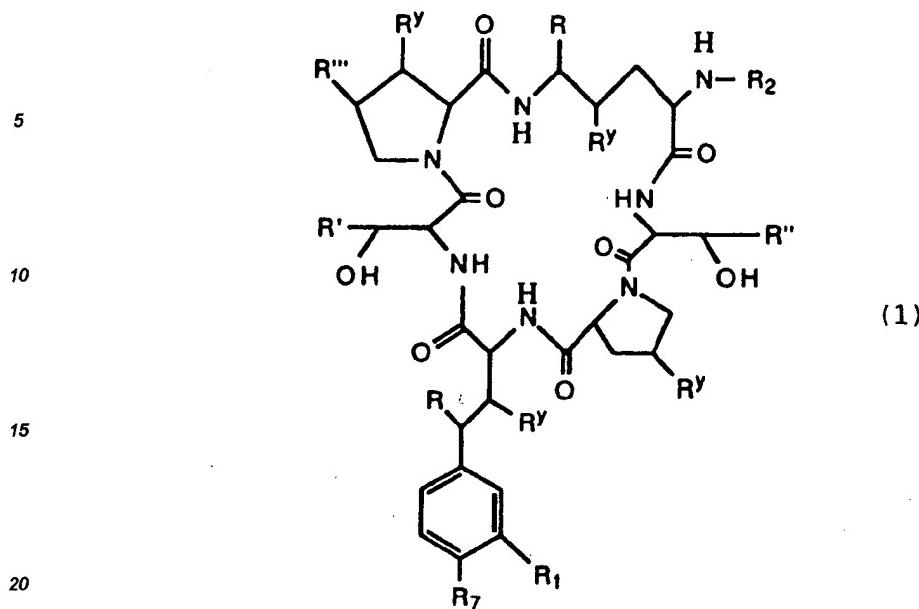
15. A compound of claims 1-11 for use in inhibiting the growth of Pneumocystis carinii.

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16. A pharmaceutical formulation comprising a compound of any of Claims 1-11 and a suitable pharmaceutical carrier.

17. A process for the preparation of a compound of the formula (1):

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wherein R' is hydrogen, methyl or $\text{NH}_2\text{C}(\text{O})\text{CH}_2$ -;

R'' and R'' is methyl or hydrogen;

25 R is hydrogen;

R^y is hydroxy or hydrogen,

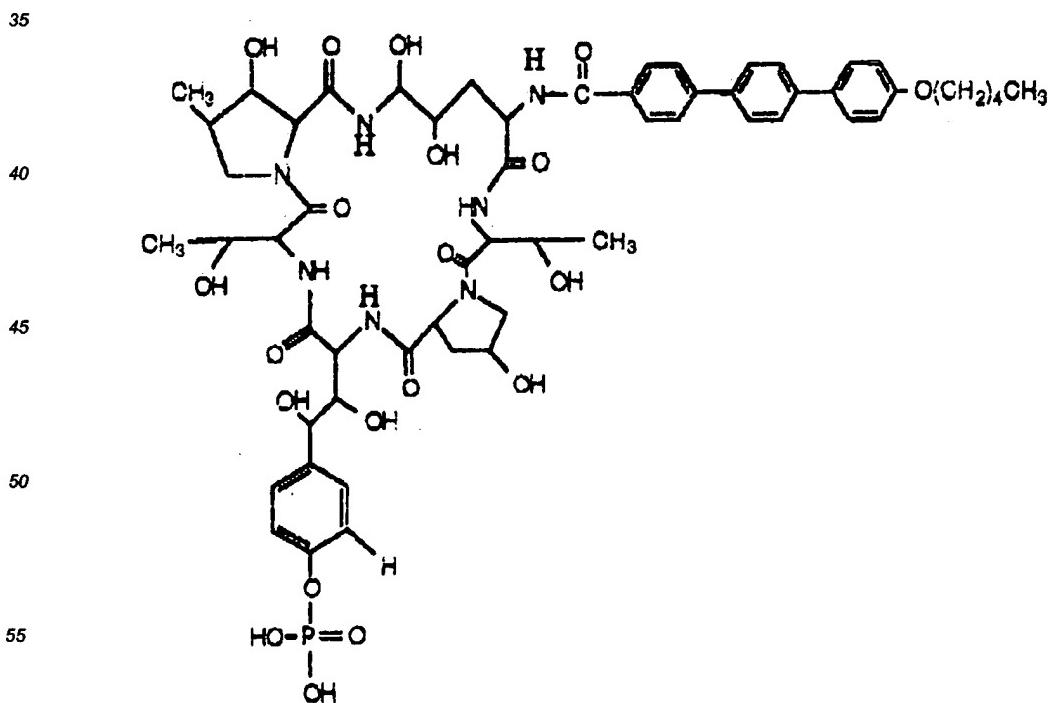
R₁ is hydroxy, or hydrogen;

R₇ is hydroxy, or hydrogen; and

R₂ is hydrogen or acyl;

30 comprising the step of subjecting a compound of formula (I) wherein R=OH, to a strong acid in the presence of a reducing agent, in a suitable solvent.

18. A compound of the formula





EUROPEAN SEARCH REPORT

Application Number

DOCUMENTS CONSIDERED TO BE RELEVANT			EP 93302064.6
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	<u>EP - A - 0 448 343</u> (MERCK & CO. INC.) * Claims 1-7 * --	1-18	C 07 K 7/56 A 61 K 37/02
A	<u>EP - A - 0 448 354</u> (MERCK & CO. INC.) * Claims 1-7 * --	1-18	
A	<u>EP - A - 0 447 186</u> (MERCK & CO. INC.) * Claims 1-7 * -----	1-18	
TECHNICAL FIELDS SEARCHED (Int. Cl.5)			
C 07 K 7/00 A 61 K 37/00			
The present search report has been drawn up for all claims			
Place of search VIENNA	Date of completion of the search 28-05-1993	Examiner SCHARF	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention 'E : earlier patent document, but published on, or after the filing date D : document cited in the application I : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			